AD_____

AWARD NUMBER: DAMD17-00-2-0018

TITLE: Mechanisms in Chronic Multisymptom Illnesses

PRINCIPAL INVESTIGATOR: Daniel J. Clauw, M.D.

CONTRACTING ORGANIZATION: University of Michigan
Ann Arbor, MI 48106

REPORT DATE: October 2009

TYPE OF REPORT: Final, Option 1

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
1 October 2009	Final, Option 1	14 Jul 2004 – 30 Sep 2009

4. TITLE AND SUBTITLE

Mechanisms in Chronic Multisymptom Illnesses

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-00-2-0018

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Daniel J. Clauw, M.D.

E-Mail: dclauw@umich.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Michigan
Ann Arbor, MI 48106

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The overall objectives of this cooperative agreement are to conduct research in pursuit of identifying the physiologic mechanisms responsible for the symptoms of pain, fatigue, and memory difficulties commonly seen in patients with Chronic Multisymptom Illnesses (CMI) (i.e., fibromyalgia, chronic fatigue syndrome, Gulf War Illnesses, etc.); to identify the risk factors for developing these syndromes as well as programs aimed at both preventing these illnesses and treating established cases. These objectives will be achieved through multiple research studies using innovative, technologically advanced (e.g., functional MRI and telemedicine) methodologies in a multidisciplinary environment. Various studies will be conducted to explore all aspects of pain processing, the effects of exercise deprivation and sleep reduction on symptomatology, the ability of exercise and/or cognitive behavioral therapies to alter patients' locus of control for pain, the neurobiological mechanism(s) of acupuncture on analgesia, the presence of hypersensitivity to auditory stimuli, and the effectiveness of cognitive behavioral therapy delivered via telemedicine and the internet. These studies will be conducted on well-characterized cohorts of CMI subjects and healthy controls taken from our burgeoning subject registry. Research continues at the University of Michigan, Ann Arbor, MI and Avera Research Institute, Sioux Falls, SD.

15. SUBJECT TERMS
chronic multisymptom illnesses, fibromyalgia, Gulf War Illness, chronic pain

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU	210	USAMRMC

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

1 INTRODUCTION 4

2 BODY 5

2.1 History of Project 5

2.2 Hypothesis and Program Objectives 5

2.3 Specific Aims 6

2.4 Research Activities 7

2.4.1 Subject Registry for Interdisciplinary Studies of CMI at The University of Michigan 7

2.4.2 The Effect of Exercise and Sleep Deprivation on the Development of CMI Symptoms 8

2.4.3 Locus of Pain Control: Neural Substrates and Modifiability 10

2.4.4 Mechanisms of Acupuncture Analgesia 13

2.4.5 Pain Mechanisms in Chronic Multisymptom Illnesses 16

2.4.6 Internet and Telehealth Enhanced CBT for the Management of Fibromyalgia 18

2.4.7 Outcome of Patients Seen in the Emergency Department after a Motor Vehicle Collision 20

2.5 Other Activities 21

2.5.1 Research Consortium, 2007 21

2.5.2 Fibromyalgia Workshop 22

2.5.3 Community Outreach Activities 22

3 KEY RESEARCH ACCOMPLISHMENTS 23

4 REPORTABLE OUTCOMES 24

4.1 Manuscripts 24

4.1.1 Peer Reviewed Publications 24

4.1.2 Non-Peer Reviewed Publications 29

4.1.3 Book Chapters and Invited Reviews 30

4.1.4 Books 32

4.2 Abstracts & Presentations 32

4.3 Patents, Licenses and Other Media 39

4.3.1 Patents and Licenses 39

4.3.2 Other Media 39

4.4 Informatics 40

4.5 Funding 40

5 CONCLUSIONS 44

6 REFERENCES 45

7 APPENDICES 50

Table of Figures

Table 1. Composition of CMI Subject Registry 7

Table 2. Composition of ESD Study Population 8

Table 3. Composition of Locus of Control Study 11

Table 4. Composition of Acupuncture Study 14

Table 5. Composition of Pain Mechanisms Study 16

Table 6. Composition of Internet and Telehealth Study 19

Table 7. Composition of MVC Study 20

1 INTRODUCTION

Researchers in the Chronic Pain and Fatigue Research Center (CPFRC) and collaborators within the National Institutes of Health, Georgetown University, the University of Michigan and the Avera Research Institute in Sioux Falls, SD worked collaboratively with Department of Army program staff to design and then implement a comprehensive clinical research program in pursuit of identifying mechanisms in Chronic Multisymptom Illnesses (CMI), including conditions such as fibromyalgia, chronic fatigue syndrome, Gulf War Illnesses etc. The research objectives include identifying:

a) the physiologic mechanisms responsible for three prominent symptoms of CMI: pain; fatigue; and memory difficulties

b) the risk factors for developing these syndromes; and

c) programs aimed at both prevention of these illnesses and treatment of established cases.

These objectives were achieved in a multidisciplinary environment and employed the use of innovative, technologically advanced methodologies, including functional MRI (fMRI), Positron Emission Tomography (PET), proton Magnetic Resonance Spectroscopy (H-MRS), assessments of sensory processing, autonomic, and hypothalamic pituitary adrenal functions, multi-dimensional patient characterization, and the use of the internet (i.e. telehealth) to disseminate educational interventions for the management of these conditions.

In summary, we feel that the funding from this Cooperative Agreement allowed our research group to do ground-breaking work on the underlying mechanisms and most effective treatments for conditions such as fibromyalgia and chronic fatigue syndrome, which are very common in the general population, and have been shown to be more common following military deployment. In large part because of our group and the work funded by the DoD, CMIs are being increasingly viewed as legitimate clinical entities by the scientific community, clinicians, and lay public – a far cry from when our funding first started.

2 BODY

2.1 History of Project

The underlying tenant of this cooperative agreement was that veterans with unexplained Gulf War Illnesses (GWI) do not suffer from any single or unique disease to the Gulf War, but instead suffer from a a constellation of symptoms and syndromes that are also seen in the general population, and variously labeled Fibromyalgia (FM), Chronic Fatigue Syndrome (CFS), and Multiple Chemical Sensitivity (MCS).

The first component of this cooperative agreement was a comprehensive, multi-disciplinary effort to study the mechanisms of CMI such as GWI, FM, CFS, and MCS. This project involved investigators formerly from Georgetown (now at the University of Michigan), Uniformed Services University for Health Services, the NIH, and several other academic institutions. The primary goal of this study was to determine the mechanism(s) responsible for expression of the three most prominent symptoms of these conditions: pain, fatigue, and memory difficulties. Physiologic factors concurrently being examined as potential causes were: aberrant afferent processing of sensory stimuli, abnormal cortical or sub-cortical central nervous system function, and disturbances of efferent neurohormonal function, including the autonomic nervous system and the hypothalamic-pituitary axes. An extensive testing protocol examining these parameters, as well as potential co-variates or confounding factors, were administered to cohorts of individuals with GWI, FM, CFS, and matched control groups.

Recruitment began in October 2000 following extensive protocol reviews and re-reviews by the Institutional Review Boards of Georgetown University, Walter Reed Army Medical Center, and the Department of the Army. From October 2000 until May 2002, significant progress was made in studying four of the original groups: FM, CFS, GWI, and controls. Beginning April 1, 2002, key personnel from CPFRC moved to the University of Michigan. The move to the University of Michigan was timed such that all of the hypotheses from the original study could be tested between these four groups, and new studies could be developed that would be performed at Michigan, retaining the most promising methodologies, and adding new collaborators.

Upon relocation to the University of Michigan, the research team focused on re-establishing itself as an active research-based Center, with additional emphasis on innovative approaches to clinical practices. The move to Michigan provided a fortuitous opportunity to overhaul the infrastructure and operating procedures required for the Center's routine research activities as well as lay foundations for future collaborative efforts. We revised our research protocols as per University of Michigan IRB requirements, taking the opportunity to streamline the subject recruitment and screening process. As a result, we were also able to broaden our studies to include not just those subjects with systemic conditions such as Gulf War Illnesses (GWI), Fibromyalgia (FM), and Chronic Fatigue Syndrome (CFS), but due to the breadth of collaborating investigators, we were also included regional conditions such as Irritable Bowel Syndrome (IBS) and Temporomandibular Disorder (TMD), conditions thought to manifest from similar underlying mechanisms.

2.2 Hypothesis and Program Objectives

Despite the administrative changes that occurred as a result of the 2002 transition to the University of Michigan, the overarching hypotheses of our group were, in essence, unchanged from the original application. We believe that:

d) Systemic conditions such as Gulf War Illnesses (GWI), Fibromyalgia (FM), and Chronic Fatigue Syndrome (CFS), and regional conditions such as Irritable Bowel Syndrome (IBS) and Temporomandibular Disorder (TMD), occur because of dysregulation of various

components of the central nervous system (CNS) including sensory processing, autonomic nervous, and neuroendocrine systems.

e) These illnesses can be triggered in susceptible individuals, and these susceptible individuals can be identified on the basis of a) a genetic predisposition, and b) differences in the function of the CNS systems noted above.

f) The environment plays a large role in determining if and when such stressors will trigger chronic illness in susceptible individuals. Along these lines, a) factors such as locus of control and level of social support are critical factors in this regard, and b) these cognitive factors have neurobiological influences on the CNS systems noted above.

Following the award of additional funds in 2001, the Center also sought to pursue the following addition hypothesis:

g) Cognitive behavioral therapy and other non-pharmacologic therapies can be effectively delivered to patients using the interactive instructional capabilities of the internet combined with occasional "in-person" group sessions using internet protocol video communications.

2.3 Specific Aims

The Specific Aims of the overarching research program at the Chronic Pain and Fatigue Research Center, as funded by the Cooperative Agreement, are:

h) to mature a registry of research subjects and healthy controls to be applied to ongoing recruitment efforts;

i) to extensively study the cognitive, psychological and neurobiological measures of pain processing in the spectrum of CMI illnesses;

j) to determine whether an established non-pharmacological intervention (Cognitive Behavioral Therapy [CBT]) is effective when administered using an internet-based educational intervention;

k) to explore both the physiologic and treatment effects of exercise and sleep on these illnesses;

l) to study the neurobiological and psychological risks for developing these illnesses after an episode of trauma (in this case motor vehicle accident);

m) to determine if individuals with FM suffer from an overall heightened sensitivity to physical stimuli (in this case auditory);

n) to examine the effects of relaxation therapy and exercise training on pain locus of control, specifically to determine whether these interventions can alter patients' pain locus of control from an external to an internal orientation;

o) to study the neurobiological mechanism(s) of acupuncture analgesia from a Western perspective on patients with FM.

These aims were addressed by seven individual research protocols, each of which is described below with a brief overview of the study and ensuing results. In addition, several peripheral activities were also undertaken at the CPFRC to support and promote its research activities. These include collaborative work with the University of Michigan GCRC to establish an offsite clinical research facility; the development of a web-based electronic data capture system to streamline the patient registrations and collection of self-reported responses to study questionnaires; varied outreach activities to regional physicians and medical providers about multi symptom illnesses such as fibromyalgia (including a 2007

conference hosted by the CPFRC at the University of Michigan); as well as bi-monthly informational and consultative workshops for CMI patients and their families.

2.4 Research Activities

2.4.1 Subject Registry for Interdisciplinary Studies of CMI at The University of Michigan

Study PI: David Williams, PhD

Study Overview

The subject registry has been consistently maintained and has functioned as the baseline screening activity for all primary studies conducted at the CPFRC. This protocol involves the development of a centralized registry that:

a) acts as a repository of interested study volunteers;

b) provides a general first-level screening of participants; and

c) matches volunteers to current or future studies for which they may be able to undergo a non-redundant and briefer study-specific screening.

Demographic information and diagnostic information is collected on each candidate regarding their general physical and psychiatric (Axis I and II) status, their specific CMI symptomatology, and the influence/interplay of CMI symptoms on their life. Under this protocol, blood samples are also collected and stored for future genetic studies of risk factors for developing these pain conditions. Future genetic studies will be funded by other mechanisms/sources under separate IRB review.

Study Population

As of September 2009, there were 599 adults enrolled in the CMI Subject Registry, comprised as follows.

	Healthy Controls	CMI
Female	167	350
Male	65	17
Total	232	367

Table 1. Composition of CMI Subject Registry

The year 2007-2008 represented the first year of our no-cost extension. Since the no-cost extension we have continued to schedule and recruit individuals into the Registry as this represents a critical resource for conducting clinical research within our Center.

Study Results

The registry is not a hypothesis driven protocol but rather an essential center resource for characterizing individuals for more efficient recruitment into other hypothesis driven protocols within our research center. With time and experience, the registry process has become more patient-friendly and efficient. When registry candidates have expressed an interest in a specific CPFRC study, all attempts are made to coordinate the scheduling of the Registry visit with the baseline visit associated with their study of interest. We have also become more diligent in describing the eligibility criteria for our various studies, which has significantly reduced the number of volunteers who complete screening but are then found to be ineligible for enrollment in other center studies.

At the close of this contract, the subject registry will be maintained under separate funding as a valuable recruiting resource.

2.4.2 The Effect of Exercise and Sleep Deprivation on the Development of CMI Symptoms

Study PI: Jennifer Glass, PhD

Study Overview

The broad aim of this study was to evaluate the individual and synergistic effects of two different lifestyle disruptions: exercise and sleep deprivation. Our underlying hypothesis is that some individuals are prone to CMI symptom development while others are not. It is this group of susceptible individuals, in this case, runners, in whom we are interested. We hypothesize that a subset of the group will present with physiological markers of an attenuated physiological stress response that acts as a diathesis for the potential development of CMI, like fibromyalgia and Gulf War Illness.

Eligible study participants included individuals between the ages of 18-40 years; who regularly ran 5 or more days per week; and who routinely slept between 7-9 hours per night. Participants were followed for a total of 24 days, including 7-days of baseline, 10-days of a restriction period, and 7-days of follow-up. Prior to restriction we evaluated autonomic nervous function, the hypothalamic pituitary adrenal axis, and symptom report. During the restriction phase participants kept daily records of pain and fatigue symptoms and completed a more detailed series of symptom questionnaires approximately 2/3 of the way through the 10-day period. During the follow-up phase, we repeated the baseline testing battery and had participants complete a final series of symptom questionnaires on their final day in the study.

Study Population

	Healthy, Active Subjects	
	Enrolled	***Included in Analyses***
Female	56	45
Male	56	42
Total	112	87

Table 2. Composition of ESD Study Population

Study Results

Recruitment for this study ended in 2006 with a total of 112 individuals accepted into the protocol, including 56 females and 56 males. Of these individuals, 95 completed participation and 17 withdrew prior to completing the study. The most common reasons for withdrawal were time constraints and unrelated illness/injury. Only 1 participant withdrew because of his group assignment (exercise deprivation). Our primary recruitment strategies were word-of-mouth and the University of Michigan's centralized clinical research site, *Engage*.

At first look, it appeared that among healthy, regularly exercising and sleeping individuals, disruption of their normal routine was associated with increased somatic symptoms. From this sample we can further suggest that a segment of healthy, symptom-free individuals possess certain baseline neurophysiological characteristics that predict subsequent symptom development. We first looked at the effect of our deprivation schemes on symptom development using a 2 (pre/post deprivation) x 2 (sleep restriction) x 2 (exercise deprivation) ANOVA. There was a significant main effect for sleep restriction for all symptom domains (pain, fatigue, mood and cognition). For example, clinical pain [$F(1,80)=8.79$,

p=.04] and fatigue [F(1,80)=37.00,p<.001] increased while mood [F(1,80)=13.41, p<.001] and perceived dyscognition worsened [F(1,80)=10.98, p=.001]. Exercise deprivation resulted in modest increases in pain, fatigue and mood, but not in dyscognition. There were no significant interactions between the two stressors.

We next explored the association between baseline (prior to deprivation) autonomic nervous system activity and symptom report. Several heart rate variability parameters were correlated with increased pain and cognition symptoms (r=-.57, p<.001) and (r=-.357, p<.05, respectively). None of these parameters were significantly associated with negative mood or increased fatigue. These preliminary findings were presented at November 2007 conference of the American College of Rheumatology.

More recent analyses of sex differences and the relationship between HRV and increased symptoms also show that sleep restriction leads to increased symptoms of pain, fatigue, mood, cognition, and somatic complaints, especially among women. Somewhat paradoxically, neurobiological measures of autonomic nervous system function were only correlated with increased symptoms in men. Our results show that women were more likely (65%) to report increased symptoms than men (40%). Among men, strong negative correlations were observed between Total Symptom Change and 24-hr total power (TP; r = -.579) as well as 24-hr ultra low frequency (ULF; r = -.628). Among women, there were no significant correlations between Total Symptom Change and any HRV measure (r values < -.180). Among men, all 5 individual symptom domains were significantly correlated with both TP and ULF (r values between -.388 and -.599). Our results are consistent with previous research on heart rate reactivity and variability to painful stimuli that suggest dramatically different sympathetic regulation of pain in men and women.

Further analyses of age and sex matched study participants (45 male, 42 female healthy adults ages 18-41 we found that women also appear much more susceptible than men to experience increased CMI symptoms particularly in the domains of mood, cognition and somatic symptoms.

By assessing symptom development in 5 domains: pain (McGill VAS), mood (CES-D, POMS, STPI-anxiety), fatigue (Multiple Fatigue Index), somatic symptoms (Modified Somatic Perceptions Questionnaire) and cognition (Multiple Ability Self-Report Questionnaire) at baseline and between days 7-8 of the deprivation period we were able to calculate a Total Symptom change variable and examine the effects of sex, sleep, and exercise were entered into examined via ANOVA. Subsequently, similar analyses were carried out for each symptom domain.

Significant effects of sleep restriction (p = .001) and sex (p = .007) were found for the Total Symptom variable. Sleep restriction resulted in more symptoms, and women were more likely to report increased symptoms. Exercise restriction did not affect Total Symptoms. Examining individual symptom domains, sleep restriction significantly increased all symptom domains (p = .008). Exercise deprivation significantly increased symptoms of fatigue (p = .021). Women reported more symptoms of negative mood (p = .016), cognition (p = .031), and somatic complaints (p = .052). Women reported increased fatigue after either exercise or sleep restriction; men reported increases only in the combined group (p = .044). A similar, but marginally significant pattern was observed for negative mood (p = .090).

The initial findings from this study were first published in 2004, as identified in the below listing. The latter findings were presented at the 2009 conference of the American College of Rheumatology.

- Glass, J.M., Lyden, A.K., Petzke, F., Stein, P., Whalen, G., Ambrose, K., Chrousos, G., and Clauw, D.J. (2004). The effect of brief exercise cessation on pain, fatigue, and mood symptom development in healthy, fit individuals. Journal of Psychosomatic Research, 57, 391-398.
- Glass, J.M., Albin K., Lyden A., Ambrose K., Gracely, R., Williams, D.A., Clauw, D.J. Sex differences in effects of sleep restriction and exercise deprivation on mood, pain, fatigue, dyscognition and somatic symptoms. *(In preparation)*

- Glass,J.M., Ablin, J., Lyden, A., Ambrose, K., Williams, D., Gracely, R, Clauw. (Oct 2009). Sex Differences in Predictors of Increased Symptoms after Exercise and Sleep Restriction. Presented at ACR/ARHP Annual Scientific Meeting
- Glass, J.M., Lyden, A., Ambrose, K., Groner, K., Gracely, R., Williams, D. Clauw, D. (May 2008). Baseline heart rate variability predicts increased pain after sleep restriction in healthy adults. Poster presented at the annual meeting of the American Pain Society, Tampa FL. *Journal of Pain, 9, Supplement 2, p. P15.*
- Glass, J.M., Lyden, A.K., Byrne-Dugan, C.J., Groner, K.H., Ambrose, K.R., Williams, D.A., Gracely R.H., Clauw, D.J. (November 2007). Effects of sleep restriction and exercise deprivation on mood, pain, fatigue, somatic symptoms and cognition in healthy adults. Poster presented at the annual meeting of the American College of Rheumatology, Boston MA. *Arthritis & Rheumatism, 56, supplemental issue, p. S93.*
- Glass, J.M., Lyden, A.K., Byrne-Dugan, C.J., Groner, K.H., Ambrose, K.R., Williams, D.A., Gracely R.H., Clauw, D.J. (November 2007). Baseline heart rate variability predicts changes in pain and cognition, but not mood or fatigue after exercise and sleep restriction. Poster presented at the annual meeting of the American College of Rheumatology, Boston MA. *Arthritis & Rheumatism, 56, supplemental issue, p. S94.*
- Glass, J.M., Lyden, A.K., Byrne-Dugan, C.J., Renard, B.M., Ambrose, K.R., Groner, K.H., Gupta, A.K., As-Sanie, S., Dadabhoy, D., Williams, D.A., Clauw, D.J. (November, 2006). Increased symptoms of pain, fatigue, cognitive problems and negative mood after exercise deprivation and sleep restriction are predicted by baseline autonomic and HPA function. Symposium presented at the annual meeting of the American College of Rheumatolgy, Washington DC. *Arthritis & Rheumatism, 54, supplemental issue.*
- Lyden, A.K., Glass, J.M., Byrne-Dugan, C.J., Renard, B.M., Gupta, A.K., As-Sanie, S., Dadabhoy, D., Williams, D.A., Clauw, D.J. (November, 2006). Pain and fatigue symptoms in healthy individuals after sleep and/or exercise restriction. Poster presented at the annual meeting of the American College of Rheumatolgy, Washington DC. *Arthritis & Rheumatism, 54, supplemental issue.*

2.4.3 Locus of Pain Control: Neural Substrates and Modifiability

Study PI: David Williams, PhD

Study Overview

This study was primarily funded through an NIAMS/NIH R01 grant (AR050044) with a small cost sharing component with this DOD cooperative agreement (DAMD 17-00-2-0018) to support some of the costs of neuroimaging.

In preliminary studies, we demonstrated that internal locus of pain control (i.e., the belief that personal effort influences pain) had a strong relationship with neurocortical activation in specific brain regions associated with pain processing and modulation (i.e. using fMRI). In these pilot investigations, individuals with greater internal locus of control not only demonstrated neurocortical changes in pain regions; but also reported lower pain ratings.

In the current study, we sought to extend these findings by using two non-pharmacological methods of increasing internal locus of pain control in individuals with fibromyalgia. Patients with fibromyalgia were randomized to receive either (a) training in relaxation, (b) training in aerobic fitness (exercise), or (c) standard care. A healthy control group was also studied. Neuroimaging was conducted at baseline and again 8 weeks later at post treatment. We hypothesized that individuals who improved internal locus of

control by any means would demonstrate lower pain report and greater neurocortical activation of pain modulatory regions at post-treatment, as evidenced by fMRI.

Study Population

	Fibromyalgia				Healthy Controls
	Relaxation	Exercise	Standard Care	Total	
Females	25	24	24	73	24
fMRI	-	-	-	57	22
Average age	*43 years*	*48 years*	*46 years*		*41 years*

Table 3. Composition of Locus of Control Study

Study Results

Recruitment for this study began in August 2005 and finished in early 2008. In total, 123 patients were approached to participate and 108 provided baseline data. Of those completing baseline, 96 subjects completed the clinical study (72 FM, and 24 HC). Of those completing the clinical study, 79 (57 FM and 22 HC) produced fMRI brain images that could be analyzed at two points in time.

The study conduct phase of this protocol required more time than originally planned (i.e., recruit and data collection). Thus both funding sources (i.e. 5R01AR50044-4 and DAMD 17-00-2-0018) went into no-cost extension during 2008. Furthermore, the leading neuroimaging faculty member for this study (i.e., Dr. Gracely) transitioned to the University of North Carolina requiring us to train new junior faculty to undertake neuroimaging analyses for this study. Remaining funds at reduced effort were allocated to the processing/analysis of neuroimaging data and the consolidation/management of clinical data from the study.

Despite these staffing setbacks, the final dataset represents an extremely valuable and unique resource from which the original study questions could be addressed and from which numerous exploratory investigations emanate. This dataset is now the largest of its kind for individuals with FM and contains an amalgam of deep multi-domain phenotyping; patient-reported outcomes and psychophysiological evoked pain testing prior to and following a non-pharmacolgical treatment trial; fMRI prior to and following a non-pharmacological treatment trial; cortisol data; and, real-time (i.e., EMA) pain ratings over an 8 week period.

The richness of this dataset enabled various analytic efforts that not only seek to address the original study questions but go beyond the original hypotheses and explore other aspects of pain modulation in FM. A listing of findings to date is summarized as follows:

- The exercise interventions had a significant impact on improving an internal locus of pain control in FM. Relaxation also appeared beneficial but did not differ significantly from the standard care condition.
- Individuals demonstrating at least a minimal improvement in internal locus of pain control (i.e., 0.5 SD improvement) did not report a decrease in clinical pain severity ratings but did demonstrate a reduction in the number of painful body regions reported at post treatment. Further, individuals demonstrating at least a minimal improvement in internal locus of pain control did report significantly greater improvements in physical functional status (an outcome that is typically more difficult to achieve than a reduction in pain). We also found that changes in mood were not associated with improvements in internal locus of pain control, and that individuals demonstrating

at least a minimal improvement in internal locus of pain control reported significantly greater improvements in fatigue, vitality and sleep.

- Previous studies from our group have identified individuals with FM to activate neurocortical regions of the pain matrix when given pressure stimuli so mild as to produce no activations in healthy controls (HC). These studies, while interesting, used relatively small sample sizes. Given the heterogeneity of FM, we sought to reconfirm these findings in a larger sample of FM versus HC. Again, in FM "mild" pressure was found to activate regions of the insula, bilateral inferior parietal lobes (BA 40), primary and secondary cortices, putamen, caudate, cerebellum, and middle frontal gyrus. Healthy controls only had activations in BA 40. In contrast to HC, mild pressure stimuli resulted in more extensive activation of pain matrix regions in individuals with FM. This study reconfirms an augmented involvement of the "pain matrix" in the processing of evoked pain in FM and supports the role of central mechanisms being responsible for the pain of FM.
- Individuals with FM who improved their internal locus of control over time demonstrated significantly stronger activation of BA40 (a region associated with semantic evaluation) and the medial prefrontal cortex (a region associated with cognition and affective evaluation). These regions are not commonly part of the pain matrix but have been associated with a second top-down network of cognitive evaluation that can influence the pain matrix.
- Individuals with FM demonstrating a change in clinical pain status between baseline and 8 weeks demonstrated either heightened activity in the pain matrix or a suppression of BOLD response to pressure stimuli that corresponded with clinical pain status supporting the use of fMRI as a biomarker for changes in pain. We also found that when no change in clinical pain occurs over time, BOLD responses to evoked pressure pain are similarly stable over time.
- In exploring the functional connectivity of neurocortical regions of individuals with FM, we found that the default mode network (i.e., the neurocortical activity of the brain in the resting-state), occupies a significantly smaller spatial extent of the cortex as pain severity increases. Furthemore, patients with FM demonstrated greater connectivity between the anterior insula and motor regions than did healthy controls; but the degree of connectivity did not correlate significantly with clinical pain, pain threshold, or anxiety.
- Some individuals with FM have widely fluctuating pain over time while others do not. Electronic pain diaries permit dense sampling of real-time pain reports that permit the calculation of the pain variability index (PVI). Greater PVI was significantly associated with greater catastrophizing and lower internal locus of control. Greater PVI was also associated with reduced BOLD activation of the PAG (a brain region associated with pain modulation), the amygala, dorsal anterior cingulated, and somatosensory cortex.
- ROI-based analysis revealed a significant difference in left anterior insula gray matter volume in individuals with FM who also had an anxiety disorder. Our results emphasize the importance of correcting for AD when carrying out VBM studies in chronic pain. Contrary to published reports with smaller sample sizes, there were no differences in cortical gray matter volume between individuals with FM and healthy controls.

Data analysis continues and presentation of results via publications and scientific conference proceedings, with several abstracts presented at the October 2009 American College of Rheumatology and Neurosciences conferences. The following list represents publications citing the major findings as detailed as above:

- Williams, DA, Patel, R., Skalski, L., Chriscinske, SJ, Rubens, M., Lapedis, J., Harris, RE, Gracely, RH, Clauw, DJ (2007). Functional MRI (fMRI) Appears to Act as a Biomarker in Fibromyalgia

(FM) by Identifying Neurobiological Correlates of Changes in Pain Over Time. Arthritis and Rheumatism, 56(9);S91-S91.

- Patel, R., Williams, DA, Gracely, RH, Skalski, L., Chriscinske, SJ, Alesi, G., Clauw, DJ (2007). Functional MRI (fMRI) of Pain Processing is Stable Over Time in Fibromyalgia (FM) Patients without Changes in Clinical Status. Arthritis and Rheumatism, 56(9);S92-S92.
- Hsu, MC, Harris, R, Sundgren PC, Welsh, RC, Fernandes, CR, Clauw DJ, Williams, DA. (2009). No consistent difference in gray matter volume between individuals with fibromyalgia and age-matched healthy subjects when controlling for affective disorder. Pain, 143;262-267.
- Williams, D.A., Glass, J.M., Barjola, P., Zwinck, L., Clauw, D. (October 2009). Cognitive Dysfunction in Fibromyalgia Assessed by the Multiple Abilities Self-Report Questionnaire. Presented at the ACR/ARHP Annual Scientific Meeting.
- Williams, D.A., Ambrose, K., Skalski, L., Muroff, J., Zwinck, L., Clauw, D. (October 2009). Improving Internal Locus of Pain Control in Fibromyalgia. Presented at the ACR/ARHP Annual Scientific Meeting.
- Ichesco, E., Bhavsar, R., Harris, R., Clauw, D., Gracely, R., Williams, D., (October 2009). Neuroimaging of Evoked Pain in Individuals with Fibromyalgia and Healthy Controls. Poster presented at the ACR/ARHP Annual Scientific Meeting.
- Harris, R., Sundgren, P., Hubbard, J., Craig, A.D., Clauw, D. (October 2009). Bilateral Anterior Insular Glutamate (Glu) is Asymmetrically Associated with Experimental Pain in Individuals with Fibromyalgia and Pain-Free Controls. Poster presented at the ACR/ARHP Annual Scientific Meeting.
- Williams, DA, Patel, R., Skalski, L., Chriscinske, SJ, Rubens, M., Lapedis, J., Harris, RE, Gracely, RH, Clauw, DJ (2007). Functional MRI (fMRI) Appears to Act as a Biomarker in Fibromyalgia (FM) by Identifying Neurobiological Correlates of Changes in Pain Over Time. Arthritis and Rheumatism, 56(9);S91-S91.
- Patel, R., Williams, DA, Gracely, RH, Skalski, L., Chriscinske, SJ, Alesi, G., Clauw, DJ (2007). Functional MRI (fMRI) of Pain Processing is Stable Over Time in Fibromyalgia (FM) Patients without Changes in Clinical Status. Arthritis and Rheumatism, 56(9);S92-S92.
- Hsu, MC, Geisser, ME, Lyden, AK, Williams, DA, Clauw, DJ (2007). Catastrophizing and Fatigue are Associated with Poorer Perceived Physical Function Relative to Objective Activity Measures in Fibromyalgia. Arthritis and Rheumatism, 56(9);S603-S603.

2.4.4 Mechanisms of Acupuncture Analgesia

Study PI: Richard E. Harris, PhD

Study Overview

In an innovative mix of modern technology and alternative therapies, we used acupuncture as a potential placebo, along with fMRI, PET, and H-MRS, to determine specific neurological mechanisms of placebo analgesia. Within this study we aimed to better define opioidergic mechanisms that underlie pain and the placebo effect.

Preliminary data, presented in the 2006-2007 progress report, suggested that patients with fibromyalgia have evidence of decreased occupancy of μ-opioid receptors at baseline within specific brain regions. This suggests that release of endogenous opioids is elevated and/or receptor numbers are low. Moreover patients with reduced receptor occupancy have elevated pain. If these findings are confirmed it may help explain why opioid drugs are not clinically effective in chronic pain conditions such as

fibromyalgia. In a separate line of research we also have shown the fibromyalgia patients have increased levels of glutamate, an excitatory neurotransmitter, within the insula, a specific brain region that encodes pain.

The major findings from this study are that:

- Fibromyalgia patients have reduced opioid receptor binding ability in brain regions known to modulate pain.
- The treatment of fibromyalgia patients with acupuncture increases mu-opioid receptor binding availability.
- Fibromyalgia patients also show elevations in insular glutamate at baseline; and
- Decreases in glutamate in this region following acupuncture and sham acupuncture, track with decreases in both clinical and experimental pain.

Study Population

	Healthy Controls	Fibromyalgia	Total
Female	15	45	60
Male	0	0	0
Total	15	45	60

Table 4. Composition of Acupuncture Study

Study Results

Initial data analyses revealed three major findings, which were presented at the 2007 conference of the American College of Rheumatology. These included:

- Using PET technology in a longitudinal study pre- and post-acupuncture or sham treatment (9 treatments over 4 weeks), significant changes in μ-opioid receptor binding potential were detected between treatment acupuncture and sham acupuncture within 17 different brain regions suggesting that the underlying mechanisms of regular acupuncture treatment and sham acupuncture treatment are not equivalent, despite similar results in clinical pain report.
- Using proton magnetic resonance spectroscopy (H-MRS) to investigate variations in glutamate (Glu) and glutamine (Gln) levels over time in FM patients, we have observed that these levels appear to change with improvements in multiple pain dimensions within FM patients.
- Finally, using H-MRS, we have shown that individuals with FM have elevated levels of glutamate within the insula and that these elevated levels are associated with increased pain sensitivity.

We also reported in abstract to national meetings in 2008-2009 that glutamate levels within the anterior insula seem to be associated with stress and anxiety whereas glutamate in the posterior insula seems to be associated with pressure pain intensity.

Overall, these findings suggest altered function within the nervous system of FM individuals. The predominant mechanisms seem to be both a reduction in inhibitory function and an increase in excitatory activity. These findings point towards specific objective abnormalities in these individuals thus giving credibility to the subjective pain report that many patients provide. Moreover these results may help in the development of new therapeutic targets for treatment. For example interventions that either up regulate inhibitory opioidergic activity or down regulate excitatory glutamatergic activity could be fruitful. Small

imaging trials of novel compounds could be performed in an effort to test efficacy prior to larger phase III randomized controlled trials, which are costly and labor intensive.

We have continued to analyze the data from this study, with four papers published since 2007 discussing these specific results, as indicated below. Furthermore, the results have contributed to the larger body of work developed by the study PI in a subsequent project entitled "Developing Biomarkers for Fibromyalgia" completed under a separate protocol also funded by the USAMRMC.

- Barjola P, Glass, J., Sundgren, P. Harte, S.E., Williams, D.A., Clauw, D., Harris, R. (October 2009) Glutamate in the Anterior Insula Is Associated with Working Memory Performance in Fibromyalgia (FM). Poster presented at the ACR/ARHP Annual Scientific Meeting.
- Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK. Decreased central mu-opioid receptor availability in fibromyalgia. J Neurosci. 2007 Sep 12;27(37):10000-6. PubMed PMID: 17855614.
- Harris RE, Sundgren PC, Craig AD, Kirshenbaum E, Sen A, Napadow V, Clauw DJ. Elevated insular glutamate in fibromyalgia is associated with experimental pain. Arthritis Rheum. 2009 Oct;60(10):3146-52. PubMed PMID: 19790053.
- Harris RE, Sundgren PC, Pang Y, Hsu M, Petrou M, Kim SH, McLean SA, Gracely RH, Clauw DJ. Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia. Arthritis Rheum. 2008 Mar;58(3):903-7. PubMed PMID: 18311814.
- Harris RE, Zubieta J-K, Scott DJ, Gracely RH, and Clauw DJ. Differential Sustained Changes in μ-Opioid Receptor (MOR) availability following Acupuncture and Sham Acupuncture Therapy in Fibromyalgia (FM). Presented to the American College of Rheumatology, 2007.
- Harris RE, Zubieta JK, Scott DJ, Napadow V, Gracely RH, Clauw DJ. Traditional Chinese acupuncture and placebo (sham) acupuncture are differentiated by their effects on mu-opioid receptors (MORs). Neuroimage. 2009 Sep;47(3):1077-85. Epub 2009 Jun 6. PubMed PMID: 19501658; PubMed Central PMCID: PMC2757074.
- Harris, RE. Sundgren, PC., Kirshenbaum, E., Xiang, Z., and Clauw, DJ. Variation in Glutamate and Glutamine Levels within the Anterior Insula are Associated with Changes in Anxiety and Pain in Fibromyalgia (FM). Presented to the American College of Rheumatology, 2008. *(See Appendix)*
- Harris, RE., Sundgren, PC., Pang, Y., Xiang, Z., Gracely, RH., Clauw, DJ., Variation in Glutamate and Glutamine Levels within the Insula are associated with Improvements in Clinical and Experimental Pain in Fibromyalgia (FM). Presented at the International Association for the Study of Pain, 2008.
- Harris, RE., Sundgren, PC., Pang, Y., Xiang, Z., Gracely, RH., Clauw, DJ., Variation in Glutamate and Glutamine levels within the Insula are Associated with Improvements in Clinical and Experimental pain in Fibromyalgia (FM). Presented to the American College of Rheumatology, 2007.
- Harrison, R.K.,Urwin, C., Bhavsar, R., Harris, R., Clauw, D., Harte, S. (October 2009.) Comparison Between Pressure and Thermal Conditioning Stimuli in the Evaluation of Descending Noxious Inhibitory Control (DNIC) in Fibromyalgia Patients and Healthy Controls. Poster presentation at the ACR/ARHP Annual Scientific Meeting.
- Poznanski, A., Hsu, M., Gracely, RH., Clauw, DJ., and Harris, RE. Differences in Central Neural Pain Processing Following Acupuncture and Sham Acupuncture Therapy in Fibromyalgia (FM). Presented to the American Pain Society, 2008.

- Poznanski, Ann, Integrative Medicine: When Main Stream Practice Embraces Alternative/Complementary Treatments, Fibromyalgia and Acupuncture: Clinical Research Update. Presented at the Michigan State Medical Society Annual Scientific Meeting, October 2008.
- Qiu, Y. Zubieta, J-K., Scott, D., Gracely, RH., Clauw, DJ. and Harris, RE. Central μ-Opioid Receptor (MOR) Availability covaries with Mood State and Pain in Fibromyalgia (FM). Presented to the American Pain Society 2008.

2.4.5 Pain Mechanisms in Chronic Multisymptom Illnesses

Study PI: Richard Gracely, PhD

Study Overview

This study aims to assess sensory processing abnormalities in CMI. Methods include various psychophysical paradigms such as ascending stimuli, random stimuli, pressure, temperature, etc., as well as fMRI to extensively examine the activity of endogenous analgesic systems. This includes descending antinociceptive activity (i.e. diffuse noxious inhibitory controls [DNIC]); aberrant afferent sensory stimuli processing; and, abnormal cortical and sub-cortical central nervous system function in groups with various CMI. This study also examines the extent to which cognitive and/or psychological processes affect pain processing in both normal individuals and individuals with these illnesses. Finally, this study will explore whether individuals with chronic pain may have a global disturbance in sensory processing by concurrently measuring auditory threshold and pain thresholds.

Study Population

	Fibromyalgia	Healthy Control
Males	3	-
Females	7	-
Total	10	23

Table 5. Composition of Pain Mechanisms Study

Study Results

This study concurrently examined neurobiological, cognitive, and psychological domains in three different CMI cohorts using the same methodologies, and not focusing only on the differences between groups, but also on the within-group differences. This approach has enabled our group to identify empirically-derived sub-groups of CMI patients. The mechanistic distinctions identified, as will as the methodologies employed in the study, have proven to be very valuable in the diagnosis and targeted treatment of individuals with this spectrum of illness. The following represents the major findings that have resulted from this study:

- Many symptoms of CMI, including as fibromyalgia and chronic fatigue syndrome, are associated with perceptual abnormalities (i.e., sensory amplification), and this deficit may be a common mechanism underlying these disorders. Treatment implications of these findings suggest that management strategies may want to focus on dampening sensory amplification, in general; rather than treating each symptom in isolation. We feel that future studies will need to replicate these findings in a larger sample as well as examine other sensory modalities such as auditory, olfactory, and visual stimuli.

- Participants with fibromyalgia displayed significantly greater sensitivity to all levels of auditory stimulation as compared to healthy controls. The magnitude of difference between fibromyalgia patients' lowered auditory sensitivity (relative to control subjects) was similar to that seen with pressure, and pressure and auditory ratings were significantly correlated in both control subjects and subjects with fibromyalgia. Fibromyalgia patients also were more sensitive to everyday sounds. These findings suggest that fibromyalgia is associated with a global central nervous system augmentation of sensory information. These findings may also help to explain why persons with fibromyalgia display a number of co morbid physical symptoms other than pain.

Functional brain imaging in fibromyalgia has revealed several key insights into

- FM patients differ from healthy controls in baseline levels of neural activity, specifically in the caudate nucleus;
- Administration of a noxious pressure or heat stimulus results in changes in brain activity consistent with the verbal reports of patients' pain intensity;
- Like healthy controls, FM patients normally detect and experience a full range of perceived pain magnitude; but sensations become unpleasant at stimulus intensities that are significantly lower than those observed in healthy controls;
- While commonly associated with chronic pain, depression does not appear to influence the sensory-discriminative dimension of pain in FM;
- Attitudes and beliefs such as locus of control and catastrophizing appear to be influential in the processing of sensory-discriminative aspects of pain;
- FM patients utilize more extensive brain resources than do same-aged peers in order to achieve comparable performance on cognitive tasks.

Pain catastrophizing, or characterizations of pain as awful, horrible and unbearable, influences pain perception through altering attention and anticipation, and heightening emotional responses to pain. Activation associated with catastrophizing in motor areas of the brain may reflect expressive responses to pain that are associated with greater pain catastrophizing. Residual scores of catastrophizing controlling for depressive symptomatology were significantly associated with increased activity in the ipsilateral claustrum ($r = 0.51$, $P < 0.05$), cerebellum ($r = 0.43$, $P < 0.05$), dorsolateral prefrontal cortex ($r = 0.47$, $P < 0.05$), and parietal cortex ($r = 0.41$, $P < 0.05$), and in the contralateral dorsal anterior cingulate gyrus (ACC; $r = 0.43$, $P < 0.05$), dorsolateral prefrontal cortex ($r = 0.41$, $P < 0.05$), medial frontal cortex ($r = 0.40$, $P < 0.05$) and lentiform nuclei ($r = 0.40$, $P < 0.05$). Analysis of subjects classified as high or low catastrophizers, based on a median split of residual catastrophizing scores, showed that both groups displayed significant increases in ipsilateral secondary somatosensory cortex (SII), although the magnitude of activation was twice as large among high catastrophizers. Both groups also had significant activations in contralateral insula, SII, primary somatosensory cortex (SI), inferior parietal lobule and thalamus. High catastrophizers displayed unique activation in the contralateral anterior ACC, and the contralateral and ipsilateral lentiform. Both groups also displayed significant ipsilateral activation in SI, anterior and posterior cerebellum, posterior cingulate gyrus, and superior and inferior frontal gyrus. These findings suggest that pain catastrophizing, independent of the influence of depression, is significantly associated with increased activity in brain areas related to anticipation of pain (medial frontal cortex, cerebellum), attention to pain (dorsal ACC, dorsolateral prefrontal cortex), emotional aspects of pain (claustrum, closely connected to amygdala) and motor control.

While recruitment for this particular study ended in 2008 at the completion of this DOD award, we continue to examine overall sensory abnormalities, as well as descending antinociceptive (DNIC) activity, in individuals with chronic pain states and in normal healthy individuals.

Data analysis continues and presentation of results via publications and scientific conference proceedings, with several abstracts presented at the 2009 American College of Rheumatology and Neurosciences conferences. The following list represents publications citing the major findings as detailed as above:

- Geisser, ME, Strader-Donnell, CS, Petzke, F, Gracely, RH, Clauw, DJ, Williams, DA. (2008). Comorbid somatic symptoms and functional status in patients with fibromyalgia and chronic fatigue syndrome: Sensory Amplification as a common mechanism. Psychosomatics, 49(3); 235-242.
- Geisser, ME, Glass, JM, Rajcevska, LD, Clauw, DJ, Williams, DA, Kileny, PR, Gracely, RH. (2008). A psychophysical study of auditory and pressure sensitivity in patients with fibromyalgia and healthy controls. Journal of Pain, 9(5); 417-422.
- Geisser ME, Gracely RH, Giesecke T, Petzke FW, Williams DA, Clauw DJ. (2007). The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome. European Journal of Pain, 11(2);202-207.
- Williams DA and Gracely RH. (2006). Biology and therapy of fibromyalgia. Functional magnetic resonance imaging findings in fibromyalgia. Arthritis Research & Therapy, 8(6);224.
- Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ (2004). Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain, 127(4); 835-843.

2.4.6 Internet and Telehealth Enhanced CBT for the Management of Fibromyalgia

(In Partnership with Avera-McKennan Research Hospital, Sioux Falls, SD)

Study PI: David Williams, PhD

Study Overview

This non-pharmacologic treatment intervention was designed to translate a successful evidence-based intervention (i.e. CBT) into an online educational format applicable to rural individuals with FM, a form of CMI. The study developed intervention materials for delivery in paper, CD-media, and internet platforms. The electronic media was used in a randomized controlled trial with outcomes focused upon pain, fatigue and overall well-bring. Two study arms were compared: (a) standard care, and (b) standard care plus the educational media. This project was designed by the investigators at the University of Michigan and the Avera-McKennan Research Hospital along with its various rural satellite clinics serving as performance sites. Given that as many as 14% of active duty personnel experience chronic symptom-based conditions and that this spectrum of illness occurred much more frequently after the Gulf War and other deployments, this project could have enormous impact on how these service members receive healthcare.

The content of the multidisciplinary educational CD covers three main topic areas: overview of fibromyalgia including a discussion of causes and treatment advice; symptom management including medications and CBT skills such as exercise, sleep, relaxation, and pleasant activities; and lifestyle management such as goal setting, problem solving, pacing, reframing, and communication. The educational CD contains standardized video lectures, homework assignments to practice skills learned, and an interactive goal tracking feature. This CD is also available as a website, which contains a chat room accessible to study participants and a link to electronic self-report forms. Web access is restricted to study participants who have signed a consent form, obtained a study identification number, and created a password. Since this site is not accessible to the general public, several screen shots have been included in the appendices to give examples of content and appearance.

Study Population

	Standard Care	Internet Education plus standard care
Males	4	3
Females	57	56
Total	61	59
Average age	50 years	50 years

Table 6. Composition of Internet and Telehealth Study

Study Results

The randomized controlled trial began in August 2006 and ended in October 2007 with the last subject completing the 6 month endpoint in April of 2008.

A total of 140 individuals with FM consented to participate in the study. Of these, 22 were screen failures resulting in 118 individuals being randomized and comprising the ITT study sample. A further 12 randomized participants terminated the study prematurely with reasons being a mixture of medical complications and participant relocation.

The groups of individuals with FM receiving the internet education in addition to their standard care demonstrated significantly improved average pain intensity when compared to those receiving standard care alone ($F_{(1, 115)}$=5.67, p<0.1). Additionally, the proportion of patients reporting a 30% decrease in mean pain score from baseline to endpoint (i.e. pain responders) was significantly greater in the group receiving supplemental internet education. Overall, about 1 in 5 patients would be expected to receive this level of benefit from the web-based intervention. This group also demonstrated statistically significant improvement in physical functional status compare to standard care ($F_{(1,115)}$=5.08, p<.03). Again, we found that 1 in 5 patients would be expected to report this level of benefit from the supplemental intervention.

Participants in the two treatment arms also differed significantly from baseline to endpoint on several factors related to sleep. While the standard care group reported significantly more mean hours of sleep than the group receiving the internet education, the adequacy of sleep obtained was reported as being significantly better by the latter group.

Overall we found that the "Living Well with FM" program was well-received by the rural sample used in this study as evidenced by the high ratings of satisfaction, improvement on outcome measures, and reported benefits. Such programs have the advantage of being available at low cost, providing high quality information without requiring a local therapist, and being accessible at the convenience of patients over the long term for a chronic condition. A modified version of "Living Well with FM" is currently available to the public through http://www.knowfibro.com/fibroguide.

At the time of this report, the following manuscript which details the findings of this study is under peer review with the journal Arthritis Care and Research:

- Williams, DA, Kuper, D, Segar, M, Mohan, N, Sheth, M, Clauw, DJ, (2009) Internet-Enhanced Management of Fibromyalgia: A Randomized Controlled Trial, Arthritis Care and Research (*Under Review*)

2.4.7 Outcome of Patients Seen in the Emergency Department after a Motor Vehicle Collision

Study PI: Samuel McLean, MD

Study Overview

This aim of this study was to examine the neurobiological and psychological predictors of chronic symptoms such as regional or widespread pain, depression, or post-traumatic stress disorder (PTSD) following a stressful traumatic event: a motor vehicle accident. Just as with the above study, our pilot data suggest that the autonomic and HPA measures taken within the Emergency Department (ED) would be predictive of the development of chronic pain or PTSD following such trauma. Individuals that are seen in the ED immediately following a motor vehicle accident that do not have a head injury, fracture or require hospitalization received an extensive testing paradigm, including psychophysical testing and psychological assessments in the ED. These individuals were then followed for 6 months and tested again at 1 and 6 months with the same paradigm. Individuals in this study also underwent fMRI testing to examine predictors of chronic pain after a traumatic event.

Study Population

	Completed 1-month evaluation	Completed 6-month evaluation	Total Enrolled
Total	126	69	140

Table 7. Composition of MVC Study

* *Study terminated 2007*

Study Results

Recruitment for this study began in early 2006. The study was terminated due in 2007 when the lead investigator, Sam McLean, left the University of Michigan and the Chronic Pain and Fatigue Research Center.

Preliminary data analysis was initial present in 2007. At the time, 126 subjects had completed the study through the 1-month follow up time point, and 69 had completed the 6-month long study. Preliminary findings indicated that demographic (age, income), symptom (pain, depression, anxiety), and cognitive (thoughts about pain and fault) characteristics affect the resolution of neck pain symptoms in patients.

Additional findings from the pilot data indicate that a relatively small number of baseline predictors provide excellent prediction of persistent musculoskeletal pain after MVC at both 1-month and 6-month follow-up. These predictors include demographic (age, race), psychological (dissociative symptoms at the time of the MVC, initial patient estimate of the time until physical recovery), physiological (general health, autonomic function), and initial symptom factors (pain, anxiety). Further exploration into racial disparity indicates that African Americans may experience a higher incidence of moderate or severe neck or back pain after MVC than European Americans. However, we recognize that further work is needed to understand this difference more completely.

These preliminary results were presented at the 2007 conference of the American College of Rheumatology. The analysis of data by the group since the departure of the lead study investigator continues and several manuscripts are expected to emanate from this study. The following is a list of publications presenting the major findings from this study:

- Zaleski, E, McLean, SA, Newton, CRH, Withrow, A., Fowler, J., Williams, DA, Stein, PK, Clauw, DJ, Liberzon, I. (2007). Emergency department physiologic predictors of pain and psychological sequelae after motor vehicle collision. Biological Psychiatry, 61(8);239S-240S.
- Switzer M, McLean SA, Jones CW, Sochor MR, Newton CRH, Withrow AD, Fowler J, Williams DA, Liberzon I, Clauw DJ. (2006). Pre-MVC Symptoms and Psychological Characteristics are Associated with Persistent Pain and Psychological Symptoms after MVC. Arthritis and Rheumatism, 54(9);S609-S609.
- Jones CW, McLean SA, Sochor MR, Newton CRH, Withrow AD, Fowler J, Stanislawski B, Williams DA, Liberzon I, Clauw DJ. (2006) Persistant Musculoskeletal Pain and Posttraumatic Stress Disorder Symptoms after Motor Vehicle Collision Share ED Symptom Risk Factors and Outcomes. Arthritis and Rheumatism, 54(9);S608-S608.
- McLean SA, Switzer M, Jones CW, Sochor MR, Newton CRH, Withrow AD, Fowler J, Williams DA, Stein PK, Liberzon I, Clauw DJ. (2006). Emergency Department Physiological Predictors of Pain and Psychological Sequelae After Motor Vehicle Collision. Arthritis and Rheumatism, 54(9);S125-S125.
- Withrow AD, McLean SA, Sochor MR, Newton CRH, Switzer M, Fowler J, Clauw DJ, Williams DA. (2006) Cognitive and Behavioral Factors Assessed 3-7 Days after Motor Vehicle Collision are Associated with Persistant Pain and Psychological Symptoms. Arthritis and Rheumatism, 54(9);S123-S124.
- Robinson D, McLean SA, Swor R, Zaleski EM, Mistry Y, Schon S, Sochor MR, Newton CRH, Liberzon I, Clauw DJ. Characteristics Associated with Neck Pain Persistence versus Recovery after Minor Motor Vehicle Collision. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.
- Schon S, McLean SA, Mistry Y, Zaleski EM, Swor R, Robinson D, Sochor MR, Newton CRH, Liberzon I, Clauw DJ. Predictors of Persistent Moderate or Severe Neck and/or Back Pain 1 and 6 Months after Minor Motor Vehicle Collision. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.
- Schon S, McLean SA, Zaleski EM, Swor R, Robinson D, Mistry Y, Sochor MR, Newton CRH, Liberzon I, Clauw DJ. Racial Disparity in Pain Outcomes after Minor Motor Vehicle Collision. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

2.5 Other Activities

2.5.1 Research Consortium, 2007

In May 2007, the CPFRC hosted a research consortium at the University of Michigan, entitled "Chronic Somatic Symptoms Consortium." UM and invited practitioners and researchers from diverse backgrounds in industry, academia and federal organizations shared their ideas on chronic pain treatment, recognition, diagnosis, research and future directions. By addressing the important role in which chronic pain treatment impacts the community – patients, clinicians, researchers, and industry – the interactions and exchanges of knowledge and ideas discussed in this consortium were aimed at leading to improved communications and collaborations regarding research, treatment and recognition for patients with chronic pain.

2.5.2 Fibromyalgia Workshop

Although not developed as a research activity, we have established center-run bi-monthly Fibromyalgia Educational Workshops at which the PI for this award provides invaluable information to the local fibromyalgia community and their families.

These workshops were initially conducted for FM patients referred from the UM Health System Division of Rheumatology, however now attendees are being referred from a wide variety of sources throughout Southeast Michigan. Over the last 6 years, more than 2000 fibromyalgia patients and their families have attended one of the educational sessions offered here at the CPFRC.

The Fibromyalgia Educational Workshops continue to be offered free of charge and all attendees receive a CD and booklet that describes a number symptom-management strategies, all of which were developed and tested as part of other CPFRC studies (such as the Internet and Telehealth study led by Dave Williams).

Given the success of this model, we are looking to expand the educational workshop to address other pain syndromes in addition to fibromyalgia. In collaboration with the UMHS Department of Gynecology, sessions targeting pelvic pain are planned for the spring of 2010. Similarly, the UMHS Department of Anesthesiology Pain Service plans to sponsor recurring sessions addressing "Central Pain Syndromes".

2.5.3 Community Outreach Activities

Throughout the funding period, members and support staff of the Chronic Pain and Fatigue Research team have participated in various campus and community-wide outreach efforts regarding fibromyalgia and related multisymptom illnesses as well as clinical research practices in general. These have included

- Speaking to the UM medical research community regarding clinical research coordinating and adverse event reporting;
- Communicating latest research findings and research opportunities to support group leaders;
- Providing education and opportunities for research participation to interested patrons of community-based health fairs and patient advocacy groups;
- Presenting abstracts at the UM Internal Medicine Research Day;
- Maintaining educational websites that focus on Gulf War Illness and chronic multisymptom illnesses including a list of the Center's publications and other reputable websites, and a description of who we are and what research opportunities exist within the Center.

3 KEY RESEARCH ACCOMPLISHMENTS

DoD funding received through this cooperative agreement has enabled two major research accomplishments for the group.

First, by employing a variety of experimental pain testing and functional neuroimaging methods, we have demonstrated that individuals with fibromyalgia have an augmented state of central nervous system pain processing. With other (non-DoD) funding, our group has shown that similar findings of diffuse hyperalgesia are also present in individuals with interstitital cystitis, low back pain, vulvodynia, and chronic pelvic pain. This work, coupled with similar studies done by other leading pain research groups, has revolutionized the pain field and led us to realize that central nervous system factors play a prominent role in many chronic pain states. In addition, it is now recognized that these conditions are best treated with tricyclics, dual reuptake inhibitors, and anticonvulsants; different classes of drugs than typically used (e.g. NSAIDs and opioids) and that non-drug therapies such as cognitive behavioural techniques and exercise are effective treatment components.

We have also made major innovations in the testing and delivery of non-pharmacological therapies in chronic pain states. We have performed seminal studies showing that even healthy young individuals will develop somatic symptoms such as pain, fatigue, and memory difficulties when deprived of routine exercise and/or sleep, and have shown for the first time that this occurs preferentially in females. We have used these data to help teach chronic pain patients why sleep, exercise, and other self-management strategies should be used in the management of their pain, and have further demonstrating that by providing education, exercise, and cognitive behavioral therapy in a web-based format we can effectively augment the management of fibromyalgia. Our findings support a significant paradigm shift and rapid movement towards patient-centric disease management approaches, rather than the classic biomedical approach, in the treatment of chronic pain.

4 REPORTABLE OUTCOMES

4.1 Manuscripts

In total, researchers from the Chronic Pain and Fatigue Research Center have produced over 100 publications since the award of this mechanism. This includes:

- 84 publications in peer-reviewed journals (including the study specific manuscripts as listed in the body of this report)
- 12 non-peer reviewed publications,
- 25 book chapters and invited review papers, and
- 3 books.

The following represents the complete list of manuscripts, in chronological order, that would not have been made possible without this cooperative agreement. *(Asterisked manuscripts are included in the appendix.)*

4.1.1 Peer Reviewed Publications

1. Naranch K, Repka-Ramirez S.M., Park YJ, Velarde A, Finnegan R, Murray J, Pheiffer A, Hwang E, Clauw DJ, Braniuk JN. Differences in baseline nasal secretions between chronic fatigue syndrome and control subjects. J of Chronic Fatigue Syndrome, 2002;10(1):3-15.
2. Williams DA, Cary MA, Groner, KH, Chaplin W, Glazer LJ, Rodriguez AM, Clauw DJ. Improving physical functional status in patients with Fibromyalgia: a brief cognitive behavioral intervention. J Rheumatol, 2002;29:1280-6.
3. Peduzzi P, Guarino P, Donta ST, Engel C, Clauw DJ, Feussner J. Research on informed consent: Investigator developed versus focus group developed consent documents, a VA cooperative study. Control Clin Trials, 2002;23(2):184-97.
4. Clauw DJ, Williams DA. The relationship between stress and pain in work-related injuries: the hidden role of chronic multisymptom illnesses. Am J Indust Med, 2002;41(5):370-82.
5. Gracely RH, Petzke F, Wolf, Clauw DJ. Functional MRI Evidence for Augmented Pain Processing in Fibromylagia. Arthritis Rheum, 2002;46(5):1333-43.
6. Crofford LJ, Clauw DJ. Fibromyalgia: where are we a decade after the American College of Rheumatology Criteria were developed? Arthritis Rheum, 2002;46(5):1136-8.
7. Donta ST, Clauw DJ, Engel CC Jr., Guarino P, Peduzzi P, Williams DA, Skinner JS, et. al. Cognitive behavioral therapy and aerobic exercise for Gulf War veteran's illnesses: a randomized controlled trial. JAMA, 2003;289(11):1396-404.
8. Petzke F, Gracely RH, Park K, Ambrose KR, Clauw DJ. What do tender points measure? Influence of distress on 4 measures of tenderness. J Rheumatol, 2003; 30(3):567-74.
9. Williams DA, Brown SC, Gendreau M, Clauw DJ. Self-reported symptoms before and after September 11 in patients with fibromyalgia. JAMA, 2003; 289(13):1637-8.
10. Petzke F, Clauw DJ, Ambrose KR, Khine A, Gracely RH. Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. Pain, 2003; 105(3):403-13.
11. Clauw DJ. Clinical research into complementary and alternative therapies: How do we tell if the glass if half-empty or half-full. J Rheumatol, 2003; 30(10):2088-9.

12. Barrett DH, Gray GC, Doebbling BD, Clauw DJ, Reeves WC. The prevalence of symptoms and symptom-based conditions among Gulf War veterans. Epidemiol. Rev, 2003; 24:218-277.

13. Clauw DJ, Crofford LJ. Chronic widespread pain and fibromyalgia: what we know, and what we need to know. Bailliere's Best Practice and Research in Clinical Rheumatology, 2003;17(4):685-701.

14. Campbell LC, Clauw DJ, Keefe FJ. Persistent Pain and Depression: A Biopsychosocial Perspective. Biol Psychiatry, 2003; 54(3):399-409.

15. Clauw DJ, Engel CC, Aronowitz R, Jones E, Kipen HM, Kroenke K, Ratzan S, Sharpe M, Wessely S. Unexplained symptoms after terrorism and war: an expert consensus statement. J Occup Environ Med, 2003; 45(10):1040-8.

16. Giesecke T, Williams DA, Harris RE, Cupps TR, Tian X, Tian TX, Gracely RH, Clauw DJ. Subgrouping of fibromyalgia patients on the basis of pressure pain thresholds and psychological factors. Arthritis Rheum, 2003; 48(10):2916-22.

17. Clauw DJ. The health consequences of the first Gulf War. British Medical Journal, 2003; 327:1357-8

18. Giesecke T, Gracely RH, Grant MAB, Nachemson A, Williams DA, Clauw DJ. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum, 2004; 50(2):613-23.

19. Giesecke J, Reed BD, Haefner HK, Giesecke T, Clauw DJ, Gracely RH. Quantitative sensory testing in vulvodynia patients reveals increased peripheral pressure pain sensitivity. Am J Obstet Gynecol, 2004; 104 (1):126-133.

20. Giesecke J, Reed BD, Haefner HK, Giesecke T, Clauw DJ, Gracely RH. Quantitative sensory testing in vulvodynia patients reveals increased peripheral pressure pain sensitivity. Am J Obstet Gynecol, 2004; 104 (1):126-133.

21. Gracely RH, Clauw DJ, Ambrose K, Petzke F. Reply to Clark's Letter. Pain, 2004; Jun; 109(3):525-526.

22. Stein PK, Domitrovich PP, Ambrose KR, Lyden AK, Fine M, Gracely RH, Clauw DJ. Sex effects on heart rate variability in fibromyalgia and Gulf War Illness. Arthritis Rheum, 2004; Oct 11;51(5):700-708.

23. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ (2004). Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain, 127(4); 835-843.

24. Glass JM, Lyden AK, Petzke F, Stein P, Whalen G, Ambrose K, Chrousos GP, Clauw DJ. The effect of brief exercise cessation on pain, fatigue, and mood symptom development in healthy, fit individuals. J Psychosom Res, 2004; Oct;57(4):391-8

25. Williams DA, Gendreau M. Hufford MR, Groner K, Gracely RH, Clauw DJ. Pain assessment in fibromyalgia syndrome: a consideration of methods for clinical trials. Clin J Pain, 2004; Sep-Oct; 20(5):348-56.

26. Williams DA, Farrell MJ, Cunningham J, Gracely RH, Ambrose K, Cupps T, Mohan N, Clauw DJ. Knee pain and radiographic osteoarthritis interact in the prediction of levels of self-reported disability. Arthritis Rheum, 2004; Aug 15:51(4):558-61.

27. Giesecke J, Reed BD, Haefner HK, Giesecke T, Clauw DJ, Gracely RH. Quantitative Sensory Testing in Vulvodynia Patients and Increased Peripheral Pressure Pain Sensitivity. Obstet Gynecol

Surv, 2004; Oct;59(10)708-709.

28. Baraniuk JN, Maibach H, Whalen G, Clauw DJ. Covariates of corticotropin releasing hormone (CRH) concentrations in cerebrospinal fluid (CSF) from healthy humans. BMC Neuroscience, 2004; 5:58.

29. Baraniuk JN, Whalen G, Cunningham J, Clauw DJ. Cerebrospinal fluid levels of opioid peptides in fibromyalgia and chronic low back pain. BMC Musculoskelet Disord, 2004; Dec 9;5(1):48.

30. Kop W, Lyden A, Berlin A, Ambrose K, Gracely RH, Williams DA, Clauw DJ. Ambulatory monitoring of physical activity and symptomatology in fibromyalgia and Chronic Fatigue Syndrome. Arthritis Rheum, 2005; Jan 7;52(1):296-303.

31. Casado B, Pannell LK, Whalen G, Clauw DJ, Baraniuk JN. Human Neuroglobin protein in cerebrospinal fluid. Proteome Sci, 2005; Feb 25;3(1):2

32. Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ. The relationship between depression, clinical pain and experimental pain in a chronic pain cohort. Arthritis Rheum, 2005; May: 52(5):1577-1584.

33. Petzke F, Harris RE, Williams DA, Clauw DJ, Gracely RH. Differences in unpleasantness induced by experimental pressure pain between patients with fibromyalgia and healthy controls. European J Pain, 2005; June: 9(3):325-35.

34. McLean SA, Williams DA, Clauw DJ. Fibromyalgia after motor vehicle collision: Evidence and implications. Traffic Injury Prevention, 2005; 6:97-104.

35. McLean SA, Clauw DJ, Abelson JL, Liberzon I. The development of persistent pain and psychological morbidity after motor vehicle collision: Integrating the potential role of stress response systems into a biopsychosocial model. Psychosomatic Medicine, 2005; Sep-Oct;67(5)783-790.

36. Harris RE, Tian X, Williams DA, Tian TX, Cupps TR, Petzke F, Groner KH, Biswas P, Gracely RH, Clauw DJ. Treatment of fibromyalgia with formula acupuncture: investigation of needle placement, needle stimulation, and treatment frequency. J Altern Complement Med, 2005; Aug;11(4)663-671.

37. McLean SA, Williams DA, Harris RE, Kop WJ, Groner KH, Ambrose K, Lyden AK, Gracely RH, Crofford LJ, Geisser ME, Sen A, Biswas P, Clauw DJ. Momentary relationship between cortisol secretion and symptoms in patients with fibromyalgia. Arthritis Rheum, 2005; Oct 28;52(11):3660-3669.

38. Harris RE, Williams DA, McLean SA, Sen A, Hufford R, Gendreau M, Gracely RH, Clauw DJ. Characterization and consequences of pain variability in individuals with fibromyalgia. Arthritis Rheum, 2005; Oct 28;52(11):3670-3674.

39. Mease PJ, Clauw DJ, Arnold LM, Goldenberg DL, Witter J, Williams DA, Simon LS, Strand CV, Bramson C, Martin S, Wright TM, Littman B, Wernicke JF, Gendreau RM, Crofford LJ. Fibromyalgia syndrome. J Rheumatol, 2005; Nov;32(11)2270-2277.

40. Dadabhoy D, Clauw DJ. Fibromyalgia: progress in diagnosis and treatment. Curr Pain Headache Rep. 2005; Dec;9(6):399-404.

41. Baraniuk JN, Casado B, Baibach H, Clauw DJ, Pannell LK, Hess SS. A Chronic Fatigue Syndrome-related proteome in human cerebrospinal fluid. BMC Neurol. 2005; Dec; 1;5:22.

42. Vit JP, Clauw DJ, Moallem T, Boudah A, Ohara PT, Jasmin L. Analgesia and hyperalgesia from CRF receptor modulation in the central nervous system of Fischer and Lewis rats. Pain. 2006 Apr;

121(3):241-60.

43. Harris RE, Gracely RH, McLean SA, Williams DA, Giesecke T, Petzke F, Clauw DJ. Comparison of Clinical and Evoked Pain Measures in Fibromyalgia. J Pain. 2006; Jul; 7(7):521-7.

44. Geisser ME, Gracely RH, Giesecke T, Petzke FW, Williams DA, Clauw DJ. The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome. Eur J Pain, 2006

45. Geisecke T, Gracely RH, Clauw DJ, Nachemson A, Duck MH, Sabatowski R, Gerbershagen HJ, Williams DA, Petzke F. Central pain processing in chronic low back pain: Evidence for reduced pain inhibition. Der Schmerz, 2006; April 4:1432-2129

46. Arguelles LM, Afari N, Buchwald DS, Clauw DJ, Furner S. Goldberg J. A twin study of posttraumatic stress disorder symptoms and chronic widespread pain. Pain, 2006

47. Bingham C, Clauw DJ, et al. Risedronate decreases biochemical markers of cartilage degredation but does not decrease symptoms or slow x-ray progression in patients with medical compartment osteoarthritis of the knee: Results of the Two-Year Multinational Knee OA Structural Arthritis (KOSTAR) Study. Arthritis Rheum, 54(11):3494-507; 2006.

48. McLean SA, Williams DA, Stein PK, Harris RE, Lyden AK, Whalen G, Park KM, Liberzon I, Sen A, Gracely RH, Baraniuk JN, Clauw DJ. Cerebrospinal fluid corticotropin-releasing factor concentration is associated with pain but not fatigue symptoms in patients with fibromyalgia. Neuropsychopharmacology. 2006 Dec;31(12):2776-82.

49. Williams DA and Gracely RH. (2006). Biology and therapy of fibromyalgia. Functional magnetic resonance imaging findings in fibromyalgia. Arthritis Research & Therapy, 8(6);224. (Included in appendix)

50. Mori DL, Sogg S, Guarino P, Skinner J, Williams D, Barkhuizen A, Engel C, Clauw D, Donta S, Peduzzi P. Predictors of exercise compliance in individuals with Gulf War veterans illnesses: Department of Veterans Affairs Cooperative Study 470. Mil Med. 2006 171(9):917-23.

51. Boyd AD, Hosner C, Hunscher DA, Athey BD, Clauw DJ, Green LA. An 'Honest Broker' mechanism to maintain privacy for patient care and academic medical research. Int J Med Inform. 2007 May-Jun;76(5-6):407-11.

52. Williams DA, Park KM, Ambrose KR, Clauw DJ. Assessor status influences pain recall. J Pain. 2007 Apr;8(4):343-8.

53. Mease, P, Arnold, L, Bennett, R, Boonen, A, Buskila, D, Carville, S, Chappell, A, Choy, E, Clauw, D, Dadabhoy, D, Gendreau, M, Goldenberg, D, Littlejohn, G, Martin, S, Perrera, P, Russell, IJ, Simon, L, Spaeth M, Williams, DA, Crofford, L. Fibromyalgia Syndrome. Journal of Rheumatology, 2007, 34(6), 1415-1425.

54. Sundgren PC, Petrou M, Harris RE, Fan X, Foerster B, Mehrotra N, Sen A, Clauw DJ, Welsh RC. Diffusion-weighted and diffusion tensor imaging in fibromyalgia patients: a prospective study of whole brain diffusivity, apparent diffusion coefficient, and fraction anisotropy in different regions of the brain and correlation with symptom severity. Acad Radiol. 2007 Jul;14(7):839-4

55. eisser ME, Gracely RH, Giesecke T, Petzke FW, Williams DA, Clauw DJ. (2007). The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome. European Journal of Pain, 11(2);202-207.

56. Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK. Decreased central mu-opioid receptor availability in fibromyalgia. J Neurosci. 2007 Sep 12;27(37):10000-6.

57. Csako G, Costello R, Shamim EA, O'Hanlon TP, Tran A, Clauw DJ, Williams HJ, Miller FW. Serum proteins and paraproteins in women with silicone implants and connective tissue disease: a case-control study. Arthritis Res Ther. 2007;9(5):R95.

58. Stein PK, Lundequam EJ, Clauw D, Freedland KE, Carney RM, Domitrovich PP. Circadian and ultradian rhythms in cardiac autonomic modulation. Conf Proc IEEE Eng Med Biol Soc 2007 Nov-Dec;26(6):14-8.

59. Harris RE, Sundgren PC, Pang Y, Hsu M, Petrou M, Kim SH, McLean SA, Gracely RH, Clauw DJ. Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia. Arthritis Rheum. 2008 Mar;58(3):903-7. PubMed PMID: 18311814.

60. Kim SH, Kim DH, Oh DH, Clauw DJ. Characteristic electron microscopic findings in the skin of patients with fibromyalgia-preliminary study. Clin Rheumatol. 2008 Feb;27(2):219-23. Murphy SL, Smith DM, Clauw DJ, Alexander NB. The impact of momentary pain and fatigue on physical activity in women with osteoarthritis. Arthritis Rheum , 2008;59(6):849-56.

61. Harris RE, Clauw DJ. Newer treatments for fibromyalgia syndrome.Ther Clin Risk Manag. 2008 Dec; 4(6):1331-42.

62. Petrou M, Harris RE, Foerster BR, McLean SA, Sen A, Clauw DJ, Sundgren PC. Proton MR spectroscopy in the evaluation of cerebral metabolism in patients with fibromyalgia: comparison with healthy controls and correlation with symptom severity. AJNR Am J Neuroradiol. 2008 May;29(5):913-8.

63. Geisser ME, Strader-Donnell C, Petzke F, Gracely RH, Clauw DJ, Williams DA. Comorbid somatic symptoms and functional status in patients with fibromyalgia and chronic fatigue syndrome: sensory amplification as a common mechanism. Psychosomatics. 2008 May-Jun;49(3):235-42.

64. Geisser, M.E., Glass, J.M., Petzke, F., Clauw, D.J., Williams, D.A., and Gracely, R.H. (2008). A psychophysical study of auditory and pressure perception in patients with fibromyalgia and healthy controls. *Journal of Pain 9 (5)* 417-422.

65. Murphy SL, Smith DM, Clauw DJ, Alexander NB. The impact of momentary pain and fatigue on physical activity in women with osteoarthritis. Arthritis Rheum. 2008 Jun 15;59(6):849-56.

66. Clauw DJ. Commentary on the EULAR recommendations for the management of fibromyalgia. Nat Clin Pract Rheumatol. 2008 Aug;4(8):392-3. Epub 2008 Jun 17.

67. Clauw DJ. Pharmacotherapy for patients with fibromyalgia. J Clin Psychiatry. 2008; 69 Suppl 2:25-9.

68. Dadabhoy D, Crofford LJ, Spaeth M, Russell IJ, Clauw DJ. Biology and therapy of fibromyalgia. Evidence-based biomarkers for fibromyalgia syndrome. Arthritis Res Ther. 2008;10(4):211. Epub 2008 Aug 8.

69. Warren JW, Howard FM, Cross RK, Good JL, Weissman MM, Wesselmann U, Langenberg P, Greenberg P, Clauw DJ. Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. Urology. 2009 Jan;73(1):52-7. .

70. Arnold LM, Bradley LA, Clauw DJ, Glass JM, Goldenberg DL. Evaluating and diagnosing fibromyalgia and comorbid psychiatric disorders. J Clin Psychiatry. 2008 Dec 3;69(10):e28.

71. Clauw DJ. Assessing and diagnosing fibromyalgia in the clinical setting. J Clin Psychiatry. 2008 Nov 6;69(11):e33. Review.

72. Geisser, ME, Glass, JM, Rajcevska, LD, Clauw, DJ, Williams, DA, Kileny, PR, Gracely, RH. (2008). A psychophysical study of auditory and pressure sensitivity in patients with fibromyalgia and healthy controls. Journal of Pain, 9(5); 417-422.

73. Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. Clin Ther. 2008 Nov;30(11):1988-2004. Erratum in: Clin Ther. 2009 Feb;31(2):446.

74. Mease PJ, Clauw DJ, Gendreau RM, Rao SG, Kranzler J, Chen W, Palmer RH. The efficacy and safety of milnacipran for treatment of fibromyalgia. a randomized, double-blind, placebo-controlled trial.J Rheumatol. 2009 Feb;36(2):398-409. Erratum in: J Rheumatol. 2009 Mar;36(3):661.

75. Clauw DJ, Witter J. Pain and rheumatology: thinking outside the joint. Arthritis Rheum. 2009 Feb;60(2):321-4.

76. Arnold LM, Bradley LA, Clauw DJ, Glass JM, Goldenberg DL. Multidisciplinary care and stepwise treatment for fibromyalgia. J Clin Psychiatry. 2009 Feb 9;69(12):e35.

77. Harris RE, Clauw DJ. Newer treatments for fibromyalgia syndrome. Ther Clin Risk Manag. 2008 Dec;4(6):1331-42.

78. Hsu MC, Harris RE, Sundgren PC, Welsh RC, Fernandes CR, Clauw DJ, Williams DA. No consistent difference in gray matter volume between individuals with fibromyalgia and age-matched healthy subjects when controlling for affective disorder. Pain. 2009 Jun;143(3):262-7.

79. Harris RE, Zubieta JK, Scott DJ, Napadow V, Gracely RH, Clauw DJ. Traditional Chinese acupuncture and placebo (sham) acupuncture are differentiated by their effects on mu-opioid receptors (MORs). Neuroimage. 2009 Sep;47(3):1077-85. Epub 2009 Jun 6. PubMed PMID: 19501658; PubMed Central PMCID: PMC2757074.

80. Harris RE, Sundgren PC, Craig AD, Kirshenbaum E, Sen A, Napadow V, Clauw DJ. Elevated insular glutamate in fibromyalgia is associated with experimental pain. Arthritis Rheum. 2009 Oct;60(10):3146-52. PubMed PMID: 19790053.

81. Williams, DA & Clauw, DJ. (2009). Understanding Fibromyalgia: Lessons from the broader pain research community. Journal of Pain, 10(8);777-791.

82. Williams, DA, Kuper, D, Segar, M, Mohan, N, Sheth, M, Clauw, DJ, Internet-Enhanced Management of Fibromyalgia: A Randomized Controlled Trial, Arthritis Care and Research *(Under Review)*

83. Glass, J.M., Albin K., Lyden A., Ambrose K., Gracely, R., Williams, D.A., Clauw, D.J. Sex differences in effects of sleep restriction and exercise deprivation on mood, pain, fatigue, dyscognition and somatic symptoms. *(In preparation)*

84. Williams, D.A., Glass, J.M., Barjola P., Zwinck, L., Clauw, D.J. Using the Multiple Abilities Self-Report Questionnaire to assess cognitive function in Fibromyalgia syndrome. *(In preparation)*

4.1.2 Non-Peer Reviewed Publications

1. Clauw DJ, Williams DA. Fibromyalgia and trauma: the issue is not whether, but why, and what can we do about it? Trauma, 2002.

2. Harris RE, Clauw DJ. The use of complementary and alternative therapies in myofascial pain disorders. Current Pain and Headache Reports, 2002;6(5):370-74.

3. Guymer EK, Clauw DJ. Treatment of fatigue in fibromyalgia. Rheum Dis Clin North Amer.

2002;28(2):367-78.

4. Clauw DJ, Simon LS. Preface. Best Pract Res Clin Pheumatol 2003; 17(4):VII-VIII.
5. Clauw DJ. Fibromyalgia: Correcting the misconceptions. J Musculoskel Med, 2003; 20(10):467-72.
6. Ambrose K, Lyden A, Clauw DJ. Applying exercise to the management of fibromyalgia. Curr Pain Headache Rep 2003; 7(5):348-54.
7. Rao S, Clauw DJ. The management of fibromyalgia. Drugs Today (Barc), 2004; June;40(6):539-554.
8. McLean SA, Clauw DJ. Predicting chronic symptoms after an acute "stressor" – lessons learned from medical conditions. Med Hypotheses, 2004; 63(4):653-8.
9. McLean SA, Clauw DJ. Biomedical models of fibromyalgia. Disability and Rehabilitation, 2005; June; 27(12):659-665.
10. Dadabhoy D, Clauw DJ. Fibromyalgia: Progress in diagnosis and treatment, 2005; Dec;9(6): 399-404.
11. Harris RE, Clauw DJ. How do we know the pain of fibromyalgia is real? Current Pain Headche Report 2007 Dec;10(6):403-7.
12. Clauw DJ. Fibromyalgia: Upadate on mechanisms and management. J Clin Rheumatol. 2007 Apr;13(2):102-9.
13. Glass, JM. (2008). Fibromyalgia and cognition. *J Clin Psychiatry, 69*; Suppl 2:20-4.

4.1.3 Book Chapters and Invited Reviews

1. Clauw DJ. Fibromyalgia associated syndromes. J Musculoskeletal Pain, 2002, 10(1/2).
2. Clauw DJ. Rheumatology for the non-rheumatologist. In: Textbook of Orthopaedics, Saunders, 2002.
3. Clauw DJ. Fibromyalgia associated syndromes, in The Clinical Neurobiology of fibromyalgia and myofascial pain: Therapeutic Implications, Robert Bennett, Editor, Haworth Press, NY, 2002.
4. Clauw DJ. Fibromyalgia and soft tissue rheumatism. In: Primer of Rheumatic Diseases, Arthritis Foundation, 2003.
5. Clauw, DJ, Williams, DA, Gracely, RH, Giesecke, T. (2004). No justification for publication of study on subgrouping of Fibromyalgia patients: comments on the article by Giesecke et al – Reply. Arthritis and Rheumatism, 50(8);2716-2717.
6. Shaikh S, Clauw DJ. Inflammatory Diseases: Diagnosis and Management. In Fromyer JW, Wiesel SW. (Eds.) The Adult and Pediatric Spine: Principles, Practice, and Surgery. Philadelphia, PA: Lippincott, Williams & Wilkins, 2004: 141-152.
7. Shaikh S, Clauw DJ. Ankylosing Spondylitis. In Lichtenstein LM, Busse WW, Geha RS. (Eds.) Current Therapy in Allergy, Immunology and Rheumatology, 6th Edition, Philadelphia, PA: Elsevier, Health Sciences Division, Mosby, 2004: 223-226.
8. Williams DA. (2004) Evaluating Pain Patients: Acute Pain. In R.H. Dworkin & W.S. Breitbart (Eds.), Psychosocial and Psychiatric Aspects of Pain: A Handbook for Health Care Providers, IASP Press, Seattle, WA;79-96
9. Williams DA. (2005) Cognitive Behavioral Therapy. In published proceedings, NIH Conference on Neuroimmune Mechanisms and Chronic Fatigue Syndrome – June 12-13, 2003. A Report of the

Scientific Workshop Co-Sponsored by the NIH Office of Research on Women's Health and the Trans-NIH Working Group for Research on Chronic Fatigue Syndrome;103-108.

10. Clauw DJ. The Taxonomy of Chronic Pain: Moving Towards More Mechanistic Classifications. In Wallace DJ, Clauw DJ. (Eds.) Textbook of Fibromyalgia and Other Central Pain Syndromes. Philadelphia, PA: Lippencott, Williams & Wilkins, 2005: 9-16.
11. Williams DA. Cognitive and Behavioral Approaches to Chronic Pain. In D.J. Wallace & D.J. Clauw (Eds.), Textbook of Fibromyalgia and Other Central Pain Syndromes. Philadelphia, PA: Lippencott, Williams & Wilkins, 2005: 343-352.
12. McLean SA, Clauw DJ, Williams DA.. The Role of Trauma in Chronic Neuromuscular Pain. In Wallace DJ, Clauw DJ. (Eds.) Textbook of Fibromyalgia and Other Central Pain Syndromes. Philadelphia, PA: Lippencott, Williams & Wilkins, 2005: 267-279.
13. Clauw DJ. The Evaluation of Individuals with Chronic Widespread Pain. In Wallace DJ, Clauw DJ. (Eds.) Textbook of Fibromyalgia and Other Central Pain Syndromes. Philadelphia, PA: Lippencott, Williams & Wilkins, 2005: 293-298.
14. McLean S, Williams DA, Clauw DJ. (2005) The Role of Trauma in Chronic Neuromuscular Pain. In D.J. Wallace & D.J. Clauw (Eds.), Textbook of Fibromyalgia and Other Central Pain Syndromes. Philadelphia, PA: Lippencott, Williams & Wilkins;267-279.
15. Clauw DJ. Innovative Treatments in CFS. In published proceedings, NIH Conference on Neuroimmune Mechanisms and Chronic Fatigue Syndrome – June 12-13, 2003. A Report of the Scientific Workshop Co-Sponsored by the NIH Office of Research on Women's Health and the Trans-NIH Working Group for Research on Chronic Fatigue Syndrome, 2005: 97-101.
16. Clauw DJ. In McCarberg B, Passik S. (Eds.) Expert Guide to Pain Management, London, United Kingdom: Royal Society of Medicine Press, 2005.
17. Clauw DJ, Harris RE. Fibromyalgia. In Boswell M, Cole B. (Eds.) Weiner's Pain Management: A Practical Guide for Clinicians, Seventh Edition. Boca Raton, FL; CRC Press, Taylor and Francis Books, Inc., 2005.
18. McLean, SA, Williams, DA, Harris, RE, Gracely, RH, Geisser, ME, Sen, A, Clauw, DJ, Crofford, LL, Kop WJ. (2006). Cortisol secretion and symptoms in patients with Fibromyalgia: comment on the article by McLean et al. – Reply. Arthritis and Rheumatism, 54(7);2346-2347.
19. Clauw DJ, Beary JF III. Fibromyalgia and Chronic Pain. In Paget SA, Gibofsy A, Beary JF III, Sculco T. (Eds.) Manual of Rheumatology and Outpatient Orthopedic Disorders, Diagnosis and Therapy, Fifth Edition. Philadelphia, PA: Lippencott, Williams & Wilkins, 2006: 409-413.
20. Clauw DJ. Fibromyalgia and Related Syndromes. In Hochberg, Silman, Smolen Weinblatt, and Weisman. (Eds.) Rheumatology, Fourth Edition. Philadelphia, PA: Elsevier, Health Sciences Division, Mosby, 2006, in press.
21. Harris RE, Clauw DJ. Chronic Widespread Pain and Fibromyalgia-What We Know and What We Need to Know. In Breivik H. and Shipley M. (Eds.) Pain: Best Practice & Research Compendium. Philadelphia, PA: Elsevier, Health Sciences Division, Mosby, 2006
22. Williams, DA. Evaluation of Function and Quality of Life in Fibromyalgia. In R. Gracely & M. Spath (Ed.s), Fibromyalgia: Assessment and Outcome, 2007 Les Entretiens du Carla;40-47.
23. Clauw DJ. Fibromyalgia. Hochberg Textbook of Rheumatology. 2007.
24. Clauw DJ. Fibromyalgia. In Bonica's Textbook of Pain. IASP Press

25. Clauw, DJ, Williams, DA. (2009). Fibromyalgia. In EA. Mayer and MC Bushnell (Eds.), Functional Pain syndromes: Presentations and Pathophysiology, IASP Press, Seattle;3-22.

4.1.4 Books

1. Wallace DJ and Clauw DJ, Eds. Fibromyalgia & Other Central Pain Syndromes. Philadelphia,PA: Lippencott, Williams & Wilkins. 2005.
2. Clauw DJ, Wallace D. Eds. Fibromyalgia 2009.
3. Clauw DJ, McCarberg W. Eds. Fibromyalgia 2009.

4.2 Abstracts & Presentations

The researchers from the Chronic Pain and Fatigue Research Center have presented at innumerable conferences since 2002, including annual American College of Rheumatology (ACR) scientific symposium, the annual American Pain Society and bi-annual International Association for the Study of Pain (IASP) conferences as well as other neuro-biological, psychological and brain mapping conferences. The following details abstracts that have been presented at the two principal conferences the American Pain Society (APS) and the American College of Rheumatology (ACR).

Presented to the American Pain Society (APS)

1. Geisser, Clauw, Strand, Gendreau, Palmer, Williams; 2009; Changes in patient global impression of hange ratings are associated with pain and other symptoms in two milnacipran clinical trials in fibromyalgia; Presented to the American Pain Society annual conference 2009.
2. R Gendreau, D Clauw, D Williams, V Strand, R Palmer; 2009; Milnacipran improves health-related quality of life in patients with fibromyalgia (FM): results from a pivotal phase III randomized controlled trial; Presented to the American Pain Society 2009.
3. K Murphy, L Pauer, D Clauw, B Herman, L Ikeda, G Atkinson, B Zeiher; 2009; Pregabalin treatment improves fatigue, function and self-reported presenteeism in fibromyalgia (FM); Presented to the American Pain Society annual conference 2009
4. M Geisser, D Clauw, R Gracely, K Ambrose, A Lyden, D Williams; 2008; Screening pain and fatigue conditions using the Complex Medical Symptoms Inventory; Presented to the American Pain Society annual conference 2008.
5. D Williams, R Gendreau, D Clauw; 2008; A comparison between electronic diaries and paper-based pain assessment in individuals with fibromyalgia (FM); Presented to the American Pain Society annual conference 2008.
6. J Glass, A Lyden, K Ambrose, K Groner, R Gracely, D Williams, D Clauw; 2008; Baseline heart rate variability predicts increased pain after sleep restriction in healthy adults; Presented to the American Pain Society annual conference 2008.
7. Y Qiu, J Zubieta, D Scott, R Gracely, D Clauw, R Harris; 2008; Central μ-Opioid Receptor (MOR) Availability Covaries with Mood State and Pain in Fibromyalgia (FM); Presented to the American Pain Society annual conference 2008.
8. M Hsu, P Sundgren, R Harris, C Fernandes, R Welsh, D Clauw; 2008; Differences in regional gray-matter density between fibromyalgia patients and controls: A voxel-based morphometry study; Presented to the American Pain Society annual conference 2008.

9. D Clauw, R Palmer, K Thacker, R Gendreau, J Gendreau, P Mease; 2008; Efficacy of milnacipran in the treatment of fibromyalgia syndrome: A 3-month, double-blind, placebo-controlled trial; Presented to the American Pain Society annual conference 2008.
10. S McLean, L Diatchenko, C Reed, C Jones, E Zaleski, Y Mistry, R Swor, M Sochor, I Liberzon, D Clauw, W Maixner; 2008; Catechol O-Methyltransferase (COMT) met/met genotype influences cortisol response and pain symptoms after minor motor vehicle collision (MVC); Presented to the American Pain Society annual conference 2008.
11. L Arnold, D Clauw, M Wohlreich, F Wang, J Ahl, P Gaynor, 2008; Efficacy of duloxetine in patients with fibromyalgia: Pooled analysis of four placebo-controlled clinical trials; Presented to the American Pain Society annual conference 2008.
12. A Poznanski, M Hsu, R Gracely, D Clauw, R Harris; 2008; Differences in central neural pain processing following acupuncture and sham acupuncture therapy in fibromyalgia (FM); Presented to the American Pain Society annual conference 2008.
13. R Harris, D Scott,R Gracely,D Clauw,J Zubieta; 2007; Differential changes in mu-opioid receptor (MOR) availability following acupuncture and sham acupuncture therapy in fibromyalgia (FM) patients; Presented to the American Pain Society annual conference 2007.
14. R Harris,D Scott, M Guevara,R Gracely,J Zubieta,D Clauw; 2007; mu-Opioid Receptor (MOR) Binding Predicts Differential Responsiveness to Acupuncture and Sham Acupuncture Therapy in Fibromylagia (FM); Presented to the American Pain Society annual conference 2007.
15. M Guevara, D Scott,J Zubieta,D Clauw,R Harris; 2007; Relationship between expectation and μ-opioid receptor (MOR) binding prior acupuncture and sham acupuncture treatment in fibromyalgia; Presented to the American Pain Society annual conference 2007.
16. M Geisser, D Williams, D Clauw; 2006; Impact of co-morbid somatic symptoms above and beyond that of pain in patients with fibromyalgia and gulf war illnesses; Presented to the American Pain Society annual conference 2007.
17. M. Geisser, D. Clauw, D. Williams, R. Patel, R. Gracely; 2005; Association between experimental and clinical pain measures in persons with fibromyalgia and chronic fatigue syndrome; Presented to the American Pain Society annual conference 2005.
18. R. Patel, D. Clauw, R. Gracely; 2005; fMRI analysis of innocuous pressure in patients with fibromyalgia; Presented to the American Pain Society annual conference 2005.
19. D. Williams, P. Biswas, J. Kalbfleisch, R. Gracely, S. Chriscinske, D. Clauw; 2004; Different aspects of daily diary symptom ratings predict clinic ratings for patients and healthy controls; Presented to the American Pain Society annual conference 2004.
20. M. Geisser, D. Williams, R. Roth, B. Patrick, D. Clauw; 2004 Levels of Pain Catastrophizing: Relationship to Categories of Pain, Disability, and Depression in Persons With Chronic Pain; Presented to the American Pain Society annual conference 2004.
21. M. Geisser, A. Lyden, K. Ambrose, D. Williams, R. Gracely, D. Clauw; 2004; Predictors of Functional Capacity Among Persons With Fibromyalgia and Chronic Fatigue Syndrome; Presented to the American Pain Society annual conference 2004.
22. Lyden, D. Williams, W. Kop, A. Berlin, R. Gracely, D. Clauw; 2004; Predictors of the low self-reported physical functioning common to fibromyalgia, chronic fatigue, and Gulf War Illnesses; Presented to the American Pain Society annual conference 2004.

23. J. Bartold, K. Ambrose, D. Clauw, T. Giesecke, D. Williams, R. Gracely; 2004; Influence of tenderness on cerebral response to equal physical pressures and equally painful pressures applied to patients with fibromyalgia (FM); Presented to the American Pain Society annual conference 2004.
24. D. Clauw, A. Lyden, J. Bartold, T. Giesecke, D. Williams, R. Gracely; 2004; Is there evidence of heightened interoception in fibromyalgia (FM)? A functional MRI (fMRI) study; Presented to the American Pain Society annual conference 2004.
25. Lyden, D. Williams, K. Groner, K. Ambrose, R. Gracely, D. Clauw; 2004; Processing of sensory sensations associated with exercise and experimental pain in fibromyalgia (FM) Presented to the American Pain Society annual conference 2004.
26. J. Glass, D. Williams, R. Gracely, D. Clauw; 2004; Relationship of self-reported pain, tender point count, and evoked pressure pain sensitivity to cognitive function in Fibromyalgia; Presented to the American Pain Society annual conference 2004.
27. R. Harris, D. Williams, X. Tian, T. Cupps, T. Giesecke, R. Gracely, D. Clauw; 2004; The influence of depression on placebo responsiveness to acupuncture in fibromyalgial; Presented to the American Pain Society annual conference 2004.
28. D. Williams, S. Brown, M. Gendreau, D. Clauw; 2003; Impact of the U.S. Terrorist Attacks on Pain and Insomnia in Patients with Preexisting Pain; Presented to the American Pain Society annual conference 2003.
29. D. Williams, K. Park, D. Clauw; 2003; Outcomes Assessment for Procedural Pain Relief: Results Depend Upon Who is Asking; Presented to the American Pain Society annual conference 2003.
30. T. Giesecke, D. Clauw, M. Grant, R. Kumar, K. Munoz, A. Nachemson, R. Gracely; 2003; Alterations in Regional Cerebral Blood Flow (RCBF) of Pain Related Brain Areas in Idiopathic Chronic Low Back Pain (ICLBP) during Evoked Pressure Pain; Presented to the American Pain Society annual conference 2003.
31. R. Harris, T. Giesecke, K. Groner, T. Cupps, X. Tian, P. Biswas, D. Williams, R. Gracely, D. Clauw; 2003; A Simplified Version of the SF-McGill Pain Questionnaire Tracks Clinical Pain in FM; Presented to the American Pain Society annual conference 2003.
32. R. Gendreau, S. Rao, D. Williams, G. Thoren, D. Clauw; 2003; Comparison of Several Pain Measurement Tools in Fibromyalgia Patients; Presented to the American Pain Society annual conference 2003.
33. M. Grant, T. Giesecke, K. Munoz, D. Clauw, R. Gracely; 2003; fMRI Analysis of Reperfusion Dysesthesia in Patients with Fibromyalgia (FM) and Healthy Control (HC) Subjects; Presented to the American Pain Society annual conference 2003.
34. T. Giesecke, D. Clauw, F. Petzke, R. Harris, T. Cupps, D. Williams, R. Gracely; 2003; Influence of Chronic Pain and Mood on Predictable and Unpredictable Pain evoked by Heat and Pressure Stimuli; Presented to the American Pain Society annual conference 2003.
35. R. Gendreau, S. Rao, G. Thoren, J. Kranzler, D. Clauw. 2003. Development Of Milnacipran, A Dual Reuptake Inhibitor For Treatment Of Chronic Pain; Presented to the American Pain Society annual conference 2003.
36. D. Williams, S. Smith, M. Cary, J. Pando, S. Mun, K. Ambrose, D. Clauw; 2003. Cognitive Behavioral Therapy Via Telemedicine for Fibromyalgia: A Pilot Study of Satisfaction For This Treatment Option; Presented to the American Pain Society annual conference 2003

37. S. Brown, S. Duke, J. Pezzullo, A. Lyden, D. Clauw, D. Williams; 2003. Cognitive Self-complexity and Health Status in Fibromyalgia (FM) Patients; Presented to the American Pain Society annual conference 2003.

Presented to the American College of Rheumatology (since 2006).

2006

1. Naylor, J.B. Romond, A.R. Bradford, D. Dadabhoy, R.H. Gracely, J. Zubieta, D.J. Clauw, (2006). Accentuated Pain Processing Despite Decreased mu-Opioid Receptor (MOR) Availability in Fibromyalgia. Presented at the 2006 American College of Rheumatology Scientific Meeting.
2. Newton, A.D. Withrow, J. Fowler, B.A. Stanislawski, D.A. Williams, I. Liberzon, D.J. Clauw. (2006). Persistent Musculoskeletal Pain and Posttraumatic Stress Disorder Symptoms After Motor Vehicle Collision Share ED Symptom Risk Factors and Outcomes (2006). Presented at the 2006 American College of Rheumatology Scientific Meeting.
3. Newton, A.D. Withrow, J. Fowler, D.A. Williams,; P.K. Stein, I. Liberzon,; D.J. Clauw, (2006) Emergency Department Physiologic Predictors of Pain and Psychological Sequelae After Motor Vehicle Collision. Presented at the 2006 American College of Rheumatology Scientific Meeting.
4. Patel, R.H. Gracely, G.A. Naylor, B.K. Michalik, L.M. Skalski, D.J. Clauw. (2006). Altered Temporal Sequences of Evoked Brain Activity in Fibromyalgia. Presented at the 2006 American College of Rheumatology Scientific Meeting.
5. Patel, B.K. Michalik, L.M. Skalski, D.J. Clauw, (2006). Stimulation Duration Alters the Initial fMRI Response to Painful Pressure in Fibromyalgia and Healthy Contols. Presented at the 2006 American College of Rheumatology Scientific Meeting.
6. Scott, G.A. Naylor, J.B. Romond, A.R. Bradford, R.H. Gracely, J. Zubieta, D.J. Clauw, (2006) Longitudinal Changes in Pressure Pain Sensitivity Vary with Insular Neuronal Activity in Fibromyalgia Patients. Presented at the 2006 American College of Rheumatology Scientific Meeting.
7. Scott, R.E. Harris, G.A. Naylor, J.B. Romond, A.R. Bradford, R.H. Gracely, D.J. Clauw, (2006). Increased mu-Opioid Receptor Availability is Detected During Clinical Pain Reduction in Fibromylagia Patients. Presented at the 2006 American College of Rheumatology Scientific Meeting.
8. Sochor, C.R. Newton, A.D. Withrow, J. Fowler, D.A. Williams, I. Liberzon, D.J. Clauw, (2006). Pre-MVC Symptom and Psychological Characteristics are Associated with Persistent Pain and Psychological Symptoms after MVC. Presented at the 2006 American College of Rheumatology Scientific Meeting.
9. Welsh, S. Krishnan, R. Patel, D.J. Clauw, (2006). .Altered Pain Functional Connectivity (fMRI) at Rest in Fibromyalgia. Presented at the 2006 American College of Rheumatology Scientific Meeting.
10. Withrow, S.A. McLean, M.R. Sochor, C.R. Newton, M. Switzer, J. Fowler, D.J. Clauw, (2006). Cognitive and Behavioral Factors Assessed 3-7 Days after Motor Vehicle Collision are Associated with Persistent Pain and Psychological Symptoms. Presented at the 2006 American College of Rheumatology Scientific Meeting.

2007

1. Clauw, K. Thacker, R. Gendreau, P. Mease, (2007). Milnacipran Efficacy in the Treatment of Fibromyalgia Syndrome: A 15-Week, Randomized, Double-Blind, Placebo-Controlled Trial . Presented at the 2007 American College of Rheumatology Scientific Meeting. Presented at the 2007 American College of Rheumatology Scientific Meeting.
2. Clauw, R.H. Palmer, O. Vitton, P. Mease, R. Gendreau, (2007). The Efficacy and Safety of Milnacipran in the Treatment of Fibromyalgia . Presented at the 2007 American College of Rheumatology Scientific Meeting. Presented at the 2007 American College of Rheumatology Scientific Meeting.
3. Clauw, M. Max, D.A. Williams, R.H. Gracely, S.A. McLean, R.E. Harris, A. Neely, E. Bair, L. Diatchenko, W. Maixner. (2007) Increased Frequency of the Minor Allele for beta-3 Adrenergic Receptors in Individuals with Fibromyalgia and Related Syndromes. Presented at the 2007 American College of Rheumatology Scientific Meeting.
4. Gendreau, D.A. Williams, R.H. Palmer, P. Mease, D.J. Clauw, (2007). Composite Responder Endpoints for Fibromyalgia Trials - Experience with Milnacipran. Presented at the 2007 American College of Rheumatology Scientific Meeting.
5. Glass, A.K. Lyden, C.J. Byrne-Dugan, K.H. Groner, K.R. Ambrose, P.J. Grace, D.A. Williams, R.H. Gracely, D.J. Clauw. (2007). Effects of Sleep Restriction and Exercise Deprivation on Mood, Pain, Fatigue, Somatic Symptoms and Cognition in Healthy Adults. Presented at the 2007 American College of Rheumatology Scientific Meeting.
6. Glass, A.K. Lyden, C.J. Byrne-Dugan, K.H. Groner, K.R. Ambrose, R.H. Gracely, D.A. Williams D.J. Clauw, (2007). Baseline Heart Rate Variability Predicts Changes in Pain and Cognition, but not Mood or Fatigue after Exercise and Sleep Restriction. Presented at the 2007 American College of Rheumatology Scientific Meeting.
7. Glass, D.C. Park, L.J. Crofford, D. Fougnie, D.J. Clauw, (2007). Working Memory in Fibromyalgia Patients: Impaired Function Caused by Distracting Information, Not Rapid Decay of Stored Information. Presented at the 2007 American College of Rheumatology Scientific Meeting.
8. Glass; R.C. Harris; P.C. Sundgren; Y. Pang; R.H. Gracely; D.J. Clauw, (2007). Variation in Glutamate and Glutamine Levels within the Inslula are associated with Improvements in Working Memory in Fibromyalgia (FM). Presented at the 2007 American College of Rheumatology Scientific Meeting.
9. Goldenberg, D.J. Clauw, R.H. Palmer, P. Mease, R. Gendreau, (2007). One-Year Durability of Response to Milnacipran Treatment for Fibromyalgia. Presented at the 2007 American College of Rheumatology Scientific Meeting.
10. Harris, J. Zubieta, D.J. Scott, L. Mayo-Bond, R.H. Gracely, D.J. Clauw, (2007). Differential Sustained Changes in ¼-Opioid Receptor (MOR) Availability Following Acupuncture and Sham Acupuncture Therapy in Fibromyalgia (FM). Presented at the 2007 American College of Rheumatology Scientific Meeting.
11. Harris, P.C. Sundgren, Y. Pang, N. Khatri, R.H. Gracely, D.J. Clauw, (2007). Variation in Glutamate and Glutamine Levels within the Insula are Associated with Improvements in Clinical and Experimental Pain in Fibromyalgia (FM) . Presented at the 2007 American College of Rheumatology Scientific Meeting.
12. Harte, S. Kim, D.J. Clauw, T.J. Morrow (2007). Altered Regional Cerebral Blood Flow at Rest in an Animal Model of Fibromyalgia . Presented at the 2007 American College of Rheumatology Scientific Meeting.

13. Hsu, M.E. Geisser, A.K. Lyden, D.A. Williams, D.J. Clauw, (2007). Catastrophizing and Fatigue are Associated with Poorer Perceived Physical Function Relative to Objective Activity Measures in Fibromyalgia. Presented at the 2007 American College of Rheumatology Scientific Meeting.
14. Hsu, S. Kim, P.C. Sundgren, Y. Pang, R.H. Gracely, D.J. Clauw, R.E. Harris. (2007). Significant Association between Changes in Glutamate Levels and fMRI BOLD Signal in the Posterior Insula of Fibromyalgia Patients. Presented at the 2007 American College of Rheumatology Scientific Meeting.
15. Mohan, D. Dadabhoy, D.J. Clauw, N.L. Henry, D.F. Hayes, V. Stearns, J.T. Giles, A. Storniolo, D. Ang, (2007) .Musculoskeletal Symptoms and Signs Associated with Aromatase Inhibitor Therapy in Breast Cancer. Presented at the 2007 American College of Rheumatology Scientific Meeting.
16. Patel, D.A. Williams, R.H. Gracely, L. Skalski, S.J. Chriscinske, G. Alesi, D.J. Clauw. (2007). Functional MRI (fMRI) of Pain Processing is Stable over Time in Fibromyalgia (FM) Patients without Changes in Clinical Status. Presented at the 2007 American College of Rheumatology Scientific Meeting.
17. Robinson, S.A. McLean, R. Swor, E.M. Zaleski, Y. Mistry, M.R. Sochor, C. Newton, I. Liberzon, D.J. Clauw, (2007). Characteristics Associated with Neck Pain Persistence versus Recovery after Minor Motor Vehicle Collision. Presented at the 2007 American College of Rheumatology Scientific Meeting.
18. Schon, S.A. McLean, Y. Mistry, E.M. Zaleski, R. Swor, D. Robinson, M.R. Sochor, C. Newton, I. Liberzon, D.J. Clauw, (2007). Predictors of Persistent Moderate or Severe Neck and/or Back Pain 1 and 6 Months after Minor Motor Vehicle Collision. Presented at the 2007 American College of Rheumatology Scientific Meeting.
19. Williams, R. Gendreau, D.J. Clauw, (2007) Electronic Diaries Have Superior Discrimination Compared to Paper-Based Pain Assessment in Individuals with Fibromyalgia. Presented at the 2007 American College of Rheumatology Scientific Meeting.
20. Williams, R. Patel, L. Skalski, S.J. Chriscinske, M. Rubens, J. Lapedis, R.E. Harris, R.H. Gracely, D.J. Clauw, (2007). Functional MRI (fMRI) Appears to Act as a Biomarker in Fibromyalgia (FM) by Identifying Neurobiological Correlates of Changes in Pain Over Time. Presented at the 2007 American College of Rheumatology Scientific Meeting.

<u>2008</u>

1. Clauw, E. Choy, P. Mease, M. Spaeth, L. Bradley, Russsell, D. Kajdasz, J. Ahl, M. Wohlreich, (2008). Impact of Duloxetine Treatment on Concentration and Mental Fatigue in Patients with Fibromyalgia. Presented at the 2008 American College of Rheumatology Scientific Meeting.
2. Clauw, M.R. Hufford, R. Zablocki, P. Qu, R.M. Gendreau, R.H. Palmer. (2008). The Effect of Milnacipran Therapy on Body Weight and Body Mass Index in Two Randomized, Double-Blind, Placebo-Controlled Trials. Presented at the 2008 American College of Rheumatology Scientific Meeting.
3. Clauw, R.H. Palmer, M.R. Hufford, R. Zablocki, Y. Wang, (2008). Milnacipran Improves Fatigue in Patients with Fibromyalgia: Results from Two Randomized, Double-Blind, Placebo-Controlled Trials. Presented at the 2008 American College of Rheumatology Scientific Meeting.
4. Harris, P.C. Sundgren, E. Kirshenbaum, Z. Xiang, D.J. Clauw,(2008). Variation In Glutamate And Glutamine Levels Within The Anterior Insula Are Associated With Changes In Anxiety And Pain

In Fibromyalgia (FM). Presented at the 2008 American College of Rheumatology Scientific Meeting.

5. Kajdasz, L.M. Arnold, A. Meyers, A.S. Chappell, D.N. D'Souza, D.J. Clauw. (2008). Dual Versus Mono Responders In Fibromyalgia Patients With Major Depressive Disorder. Presented at the 2008 American College of Rheumatology Scientific Meeting.
6. Lee, L.B. Chibnik, A.H. Fossel, D.H. Solomon, D.J. Clauw, E.W. Karlson, (2008). The Reproducibility of Dolorimetry Measurements in Rheumatoid Arthritis Patients. Presented at the 2008 American College of Rheumatology Scientific Meeting.
7. Mease, M. Spaeth, D.J. Clauw, L.M. Arnold, L.A. Bradley, I.J. Russell, D.K. Kajdasz, D.J. Walker, (2008). Estimation of Minimum Clinically Important Difference of Pain in Fibromyalgia. Presented at the 2008 American College of Rheumatology Scientific Meeting.
8. Wolfe, D.J. Clauw, D.L. Goldenberg, R.S. Katz, (2008). Toward the Development of Revised Criteria for the Fibromyalgia Diagnosis. Presented at the 2008 American College of Rheumatology Scientific Meeting.

2009

1. Ablin, Cohen, Clauw, Shalev, Ablin, Neumann and Buskila. (2009). A Tale of Two Cities – the Effect of Low Intensity Conflict On Prevalence and Characteristics of Musculoskeletal Pain Associated with Chronic Stress. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.
2. Glass, Ablin, Lyden, Ambrose, Williams, Clauw and Byrne-Dugan,(2009). Women Are More Susceptible to Increased Symptoms of Pain, Fatigue, Negative Mood, and Cognitive Dysfunction After Exercise and Sleep Restriction. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.
3. Glass, Ablin, Lyden, Ambrose, Williams, Gracely and Clauw. (2009). Sex Differences in Predictors of Increased Symptoms After Exercise and Sleep Restriction (ACR/ARHP Annual Scientific Meeting)
4. Gore, Sadosky, Zlateva and Clauw, (2009).Patterns of Pain-Related Pharmacotherapy and Healthcare Resource Use Among Elderly Patients with Fibromyalgia Prescribed Pregabalin. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.
5. Harris, Clauw, Ichesco, Geisser and Williams,(2009). Neurobiological Correlates of Spontaneous Chronic Pain Variability. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.
6. Harris, Sundgren, Hubbard, Craig and Clauw, (2009). Bilateral Anterior Insular Glutamate (Glu) Is Asymmetrically Associated with Experimental Pain in Individuals with Fibromyalgia and Pain-Free Controls. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.
7. Harrison, Urwin, Bhavsar, Harris, Clauw and Harte, (2009). Comparison Between Pressure and Thermal Conditioning Stimuli in the Evaluation of Descending Noxious Inhibitory Control (DNIC) in Fibromyalgia Patients and Healthy Controls. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.
8. Harte, Zwinck, Gendreau, Williams, Clauw and Harris (2009). Fluctuations in Baseline Clinical Pain Intensity Predict Therapeutic Response to Milnacipran in Patients with Fibromyalgia. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.
9. Hassett, Clow, Williams and Clauw,(2009). Cortisol Awakening Response and Affective Factors in Fibromyalgia. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.

10. Ichesco, Bhavsar, Harris, Clauw, Gracely and Williams. (2009). Neuroimaging of Evoked Pain in Individuals with Fibromyalgia and Healthy Controls. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.
11. Lee, Chibnik, Lu, Wasan, Edwards, Fossel, Helfgott, Solomon, Clauw and Karlson. (2009) The Relationship Between Disease Activity, Sleep, Psychiatric Distress and Pain Sensitivity in Rheumatoid Arthritis. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.
12. Palmer, Clauw, Mainguy, Wang and Gendreau, (2009). Baseline Characteristics of Fibromyalgia Patients in 4 Clinical Trials of Milnacipran. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.
13. Williams, Ambrose, Skalski, Muroff, Zwinck and Clauw, (2009). Improving Internal Locus of Pain Control in Fibromyalgia. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.
14. Williams, Glass, Barjola, Zwinck and Clauw, (2009). Cognitive Dysfunction in Fibromyalgia Assessed by the Multiple Abilities Self-Report Questionnaire. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.
15. Williams, Harris, Bhavsar, Clauw, Zubieta and Gracely, (2009). Neurocortical Representation of Locus of Control in Individuals with Fibromyalgia. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.
16. Wolfe, Clauw, Fitzcharles, Goldenberg, Harp, Katz, Mease, Michaud, Russell, Russell, Winfield and Yunus (2009). The Instability of Fibromyalgia Diagnosis: Associations with Measures of Severity. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.
17. Wolfe, Clauw, Fitzcharles, Goldenberg, Harp, Katz, Mease, Michaud, Russell, Russell, Winfield and Yunus, (2009). Clinical Diagnostic and Severity Criteria for Fibromyalgia. Presented at the 2009 ACR/ARHP Annual Scientific Meeting.

4.3 Patents, Licenses and Other Media

4.3.1 Patents and Licenses

In 2008 Eli Lilly and Company, together with the National Fibromyalgia Association licensed the use of the "Living Well with FM" web-based intervention program used in the Internet and Telehealth Enhanced CBT study. As a result, a modified version of the program is now publicly available through http://www.knowfibro.com . Screenshots of both "Living Well with FM" and the KnowFibro website can be found in the appendix.

4.3.2 Other Media

1. Gulf War Health: Coming Home from War. A web site dedicated to supplying information to returning soldiers, their families, and health professionals about post-deployment health. http://www.med.umich.edu/gulfwarhealth, (2003)
2. Williams, D.A. (2003) Patient Self-Esteem, Fibromyalgia Network.
3. Williams, D.A. (2003) Cognitive Behavioral Therapy: A Strategy to Assist in the Management of Fibromyalgia, Fibromyalgia Aware.
4. Williams, D.A. (2004) Patient Expectations, Fibromyalgia Network.
5. Williams, D.A. (2005). Live Well with Fibromyalgia: Educational Workbook. Chronic Pain and Fatigue Research Center, University of Michigan Health System, University of Michigan [Workbook, website, and CD-media].

6. Clauw DJ. (2005) New Insights into the Pathophysiology of Fibromyalgia. Exploring Fibromyalgia monograph. CME activity. Center for Health Care Education.
7. Williams, DA (2008). Research-Supported Treatments for Chronic Pain. In E.D. Klonsky (Ed.), Division 12, American Psychological Association website on research supported-treatments.
8. Williams, DA (2009). Promising new innovations in assessing Fibromyalgia. Fibromyalgia Aware

4.4 Informatics

While no technologies were developed as a direct result from the DoD funded studies. Researchers from the CPFRC were the primary drivers behind the University of Michigan developed web-based survey database, *BiodBx*. This platform was developed to enable the electronic delivery of standardized self-report forms throughout all the DoD, and other, funded studies.

4.5 Funding

The following details all funding opportunities awarded and applied for based on work supported by this award.

Faculty Member(s): Clauw (Co-Investigator)
Project Title: Vagus Nerve Stimulation in Fibromyalgia
Sponsor: NIH **Project ID**: R01 AR053732 (Lange)
Project Period: 9/16/05-6/30/10
Total Project Amount:
Award Status: Awarded

Faculty Member(s): Clauw (Co-Investigator)
Project Title: DNA Analysis in Multi-Phase Microfabricated Devices
Sponsor: NIH **Project ID**: R01 EB006789 (Burns)
Project Period: 8/01/08-7/31/11
Total Project Amount:
Award Status: Awarded

Faculty Member(s): Clauw (Consultant)
Project Title: Lifestyle Physical Activity for Fibromyalgia
Sponsor: NIH **Project ID**: R01 AR053168 (Fontaine)
Project Period: 7/15/06-5/31/10
Total Project Amount:
Award Status: Awarded

Faculty Member(s): Clauw (Mentor)
Project Title: Neurobiological Mechanisms behind Pain Modulation in Subtypes of Fibromyalgia
Sponsor: NIH/NICHD **Project ID**: K12 HD001097 (Trainee: Michael Hsu, M.D., P.I: Boninger)
Project Period: 7/7/08-7/6/11
Total Project Amount:
Award Status: Awarded

Faculty Member(s): Clauw (Mentor)
Project Title: Endometriosis Immunomodulation and Allo-Autoimmunity
Sponsor: NIH **Project ID**: K23 HD043952 (LeBovic)

Project Period: 5/01/05-4/30/10
Total Project Amount:
Award Status: Awarded

Faculty Member(s): Clauw (PI), Williams (Co-Investigator)
Project Title: University of Michigan CTSA – The Michigan Institute for Clinical & Health Research (MICHR)
Sponsor: NIH / NCRR **Project ID**: UL1 RR024986
Project Period: 9/17/07-5/31/12
Total Project Amount:
Award Status: Awarded

Faculty Member(s): Clauw (PI), Williams (Co-Investigator), Harris (Co-Investigator)
Project Title: Multi-disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network Discovery Site
Sponsor: NIH / NIDDK **Project ID**: U01 DK082345
Project Period: 9/15/08–6/30/13
Total Project Amount:
Award Status: Awarded

Faculty Member(s): Clauw (PI), Williams (Co-Investigator), Harris (Co-Investigator), Harte (Co-Investigator),
Project Title: A Single-center, Randomized, Double-blind, Placebo-controlled, Two-way Crossover Study to Evaluate the effect of Milnacipran on Pain Processing in Patients with Fibromyalgia: An fMRI Study.
Sponsor: Forest Research Laboratories, Inc **Project ID**: Protocol #MLN-MD-16
Project Period: 11/10/08-5/30/10
Total Project Amount:
Award Status: Awarded

Faculty Member(s): Harris (PI)
Project Title: Distinct Roles of Anterior and Posterior Insula Glutamate in Chronic Pain
Sponsor: Dana Foundation Grant
Project Period: 03/2009 – 03/2012
Total Project Amount:
Award Status: Awarded

Faculty Member(s): Williams (PI)
Project Title: Development of a Fibromyalgia Responder Index.
Sponsor: NIAMS/NIH **Project ID**: R01 AR053207-01A2 (Arnold)
Project Period: 4/1/07 – 3-31/10
Total Project Amount:
Award Status: Awarded

Faculty Member(s): Williams (PI)
Project Title: A Fibromyalgia-Specific Extension of the PROMIS Network.
Sponsor: NIH/NIAMS **Project ID**: U01 AR55069-01
Project Period: 04/01/07 - 03/31/10
Total Project Amount:

Award Status: Awarded

Faculty Member(s): Clauw (Consultant)
Project Title: An outcome study of rheumatoid hand arthroplasty
Sponsor: NIH **Project ID**: R01 AR0473280 (Chung)
Project Period: 9/08/03-8/31/09
Total Project Amount:
Award Status: Completed

Faculty Member(s): Clauw (Mentor)
Project Title: Clinical Strategies to Reduce Osteoarthritis Disability
Sponsor: NIH **Project ID**: K01 HD045293
Project Period: 9/1/04-8/31/09
Total Project Amount:
Award Status: Completed

Faculty Member(s): Harris (PI)
Project Title: Mechanisms of Acupuncture Analgesia
Sponsor: NIH **Project ID**: 1KO1 AT01111-01
Project Period: 09/01/02-02/28/08
Total Project Amount:
Award Status: Completed

Faculty Member(s): Harris (PI), Clauw (Co-Investigator)
Project Title: Developing Biomarkers for Fibromyalgia
Sponsor: DoD **Project ID**: PR064072
Project Period: 11/9/06-11/8/09
Total Project Amount:
Award Status: Completed

Faculty Member(s): Harris (PI), Clauw (Consultant)
Project Title: Effect of Pregabalin on Brain Functional Magnetic Resonance Imaging, Proton Magnetic Resonance Spectroscopy, and Subjective Pain Response to Experimentally-Induced Mechanical and Thermal Pain in Patients with Fibromyalgia
Sponsor: Pfizer Global Research and Development **Project ID**: A0081211
Project Period: 12/01/08-10/31/09
Total Project Amount:
Award Status: Completed

Faculty Member(s): Williams (Co-Investigator)
Project Title: Focused Integrative Coping Strategies (FICS) for Sailors: Follow-up Intervention Study
Sponsor: NIH **Project ID**: N04-014
Project Period: 5/1/04-4/30/07
Total Project Amount:
Award Status: Completed

Faculty Member(s): Williams (Consultant)
Project Title: Chronic Low Back Pain as a Model of Fibromyalgia

Sponsor: NIH **Project ID**: RO1 AR46049
Project Period: 6/1/99-5/31/04
Total Project Amount:
Award Status: Completed

Faculty Member(s): Williams (Mentor)
Project Title: Development of Chronic Pain after Motor Vehicle Trauma.
Sponsor: NIH **Project ID**: K23 KAR050410A (McLean)
Project Period: 7/1/06-6/30/09
Total Project Amount:
Award Status: Completed

Faculty Member(s): Williams (Mentor)
Project Title: Motivational Feedback to Increase Walking Adherence.
Sponsor: NIH/NHLBI **Project ID**: K-23-HL0750980-02 (Richardson)
Project Period: 9/30/04 - 8/31/09
Total Project Amount:
Award Status: Completed

Faculty Member(s): Williams (PI)
Project Title: Locus of Pain Control: Neural Substrates and Modifiability
Sponsor: NIAMS/NIH **Project ID**: R01 AR050044
Project Period: 5/19/04-03/31/09
Total Project Amount:
Award Status: Completed

Faculty Member(s): Clauw
Project Title: Pain and Musculoskeletal Disorders: Translating Scientific Advances into Practice
Sponsor: NIH/NIAMS **Project ID**: U13 AR0580639
Project Period: 9/15/09–3/15/10
Total Project Amount:
Award Status: Pending

Faculty Member(s): Williams (PI), Clauw (Co-Investigator)
Project Title: Comparative Effectiveness of Medication and Behavioral Management of Fibromyalgia
Sponsor: NIH/NIAMS **Project ID**: RC1 (MPI)
Project Period: 9/30/09-9/29/11
Total Project Amount:
Award Status: Pending

5 CONCLUSIONS

In summary, we feel that the funding from this Cooperative Agreement allowed our research group to do ground-breaking work on the underlying mechanisms and most effective treatments for conditions such as fibromyalgia and chronic fatigue syndrome, which are very common in the general population, and have been shown to be more common following military deployment.

In large part because of our group and the work funded by the DoD:

- The experimental pain testing and brain imaging studies performed by our group are highly cited and have helped convince many scientists, clinicians, funding agencies, and individuals in the lay public that conditions such as fibromyalgia are legitimate entities with strong neurobiological underpinnings.
- This work helped convince the pharmaceutical industry to pursue drug development in fibromyalgia, leading to three drugs being approved specifically for this condition.
- Primarily using non-DoD funding, our group and others have shown that some of the same neurobiological mechanisms that are operative in fibromalgia (e.g. hyperalgesia, diffuse sensory augmentation) are also seen in most other chronic pain states, which has been even more helpful in de-stigmatizing fibromyalgia.

Because of the DoD funding of the Living Well with Fibromyalgia website and the successful clinical trail showing the effectiveness of this as a stand-alone therapy, many in the pain field are taking our lead and developing web-based programs such as this to augment the care of chronic pain patients.

6 REFERENCES

The following is a list of all publications referred to in the body of this report. Unless otherwise indicated, copies of these publications can be found in the appendix.

Peer-Reviewed Journal Publications

1. Geisser ME, Gracely RH, Giesecke T, Petzke FW, Williams DA, Clauw DJ. (2007). The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome. European Journal of Pain, 11(2);202-207. PMID: 16546424
2. Geisser, ME, Glass, JM, Rajcevska, LD, Clauw, DJ, Williams, DA, Kileny, PR, Gracely, RH. (2008). A psychophysical study of auditory and pressure sensitivity in patients with fibromyalgia and healthy controls. Journal of Pain, 9(5); 417-422.
3. Geisser, ME, Strader-Donnell, CS, Petzke, F, Gracely, RH, Clauw, DJ, Williams, DA. (2008). Comorbid somatic symptoms and functional status in patients with fibromyalgia and chronic fatigue syndrome: Sensory Amplification as a common mechanism. Psychosomatics, 49(3); 235-242.
4. Glass, J.M., Albin K., Lyden A., Ambrose K., Gracely, R., Williams, D.A., Clauw, D.J. Sex differences in effects of sleep restriction and exercise deprivation on mood, pain, fatigue, dyscognition and somatic symptoms. *(Not available - in preparation)*
5. Glass, J.M., Lyden, A.K., Petzke, F., Stein, P., Whalen, G., Ambrose, K., Chrousos, G., and Clauw, D.J. (2004). The effect of brief exercise cessation on pain, fatigue, and mood symptom development in healthy, fit individuals. Journal of Psychosomatic Research, 57, 391-398.
6. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ (2004). Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain, 127(4); 835-843.
7. Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK. Decreased central mu-opioid receptor availability in fibromyalgia. J Neurosci. 2007 Sep 12;27(37):10000-6. PubMed PMID: 17855614.
8. Harris RE, Sundgren PC, Craig AD, Kirshenbaum E, Sen A, Napadow V, Clauw DJ. Elevated insular glutamate in fibromyalgia is associated with experimental pain. Arthritis Rheum. 2009 Oct;60(10):3146-52. PubMed PMID: 19790053.
9. Harris RE, Sundgren PC, Pang Y, Hsu M, Petrou M, Kim SH, McLean SA, Gracely RH, Clauw DJ. Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia. Arthritis Rheum. 2008 Mar;58(3):903-7. PubMed PMID: 18311814.
10. Harris RE, Zubieta JK, Scott DJ, Napadow V, Gracely RH, Clauw DJ. Traditional Chinese acupuncture and placebo (sham) acupuncture are differentiated by their effects on mu-opioid receptors (MORs). Neuroimage. 2009 Sep;47(3):1077-85. Epub 2009 Jun 6. PubMed PMID: 19501658; PubMed Central PMCID: PMC2757074.
11. Hsu, MC, Harris, R, Sundgren PC, Welsh, RC, Fernandes, CR, Clauw DJ, Williams, DA. (2009). No consistent difference in gray matter volume between individuals with fibromyalgia and age-matched healthy subjects when controlling for affective disorder. Pain, 143;262-267. PMCID: 2719961
12. Williams DA and Gracely RH. (2006). Biology and therapy of fibromyalgia. Functional magnetic resonance imaging findings in fibromyalgia. Arthritis Research & Therapy, 8(6);224. PMCID: 1794529

13. Williams, DA, Kuper, D, Segar, M, Mohan, N, Sheth, M, Clauw, DJ, Internet-Enhanced Management of Fibromyalgia: A Randomized Controlled Trial, Arthritis Care and Research *(Under Review)*

Abstract Presentations

1. Barjola P, Glass, J., Sundgren, P. Harte, S.E., Williams, D.A., Clauw, D., Harris, R. (October 2009) Glutamate in the Anterior Insula Is Associated with Working Memory Performance in Fibromyalgia (FM). Poster presented at the ACR/ARHP Annual Scientific Meeting.

2. Geisser ME, Clauw DJ, Williams DA, Patel R, Gracely RH. (2005). Association between Experimental and Clinical Pain Measures in Persons with Fibromyalgia and Chronic Fatigue Syndrome. Journal of Pain (abstract supplement), 6, 3, S26. Presented at the 24th Annual Scientific Meeting of the American Pain Society.

3. Glass, J.M., Lyden, A., Ambrose, K., Groner, K., Gracely, R., Williams, D. Clauw, D. (May 2008). Baseline heart rate variability predicts increased pain after sleep restriction in healthy adults. Poster presented at the annual meeting of the American Pain Society, Tampa FL. *Journal of Pain, 9, Supplement 2, p. P15.*

4. Glass, J.M., Lyden, A.K., Byrne-Dugan, C.J., Groner, K.H., Ambrose, K.R., Williams, D.A., Gracely R.H., Clauw, D.J. (November 2007). Effects of sleep restriction and exercise deprivation on mood, pain, fatigue, somatic symptoms and cognition in healthy adults. Poster presented at the annual meeting of the American College of Rheumatology, Boston MA. *Arthritis & Rheumatism, 56, supplemental issue, p. S93.*

5. Glass, J.M., Lyden, A.K., Byrne-Dugan, C.J., Groner, K.H., Ambrose, K.R., Williams, D.A., Gracely R.H., Clauw, D.J. (November 2007). Baseline heart rate variability predicts changes in pain and cognition, but not mood or fatigue after exercise and sleep restriction. Poster presented at the annual meeting of the American College of Rheumatology, Boston MA. *Arthritis & Rheumatism, 56, supplemental issue, p. S94.*

6. Glass, J.M., Lyden, A.K., Byrne-Dugan, C.J., Renard, B.M., Ambrose, K.R., Groner, K.H., Gupta, A.K., As-Sanie, S., Dadabhoy, D., Williams, D.A., Clauw, D.J. (November, 2006). Increased symptoms of pain, fatigue, cognitive problems and negative mood after exercise deprivation and sleep restriction are predicted by baseline autonomic and HPA function. Symposium presented at the annual meeting of the American College of Rheumatolgy, Washington DC. *Arthritis & Rheumatism, 54, supplemental issue.*

7. Glass,J.M., Ablin, J., Lyden, A., Ambrose, K., Williams, D., Gracely, R, Clauw. (Oct 2009). Sex Differences in Predictors of Increased Symptoms after Exercise and Sleep Restriction. Presented at ACR/ARHP Annual Scientific Meeting

8. Gracely RH, Patel R, Harte SE, Clauw DJ. (2006). Dynamic DNIC activation of vPAG in human subjects. Presented at 2006 Society for Neuroscience *(not available)*

9. Gracely, RH. (2006) DNIC activation of vPAG is Adsent ion Fibromyalgia. Presented at the 2006 American College of Rheumatology

10. Harris RE, Scott DJ, Naylor GA, Romond JB, Bradford AR, Dadabhoy D, Gracely RH, Zubieta J-K, Clauw DJ. (2006). Accentuated Pain Processing Despite Decreased mu-Opioid Receptor (MOR) Availability in Fibromyalgia. Presented at the 2006 American College of Rheumatology

11. Harris RE, Scott DJ, Naylor GA, Romond JB, Bradford AR, Gracely RH, Zubieta J-K, Clauw DJ. (2006). Longitudinal Changes in Pressure Pain Sensitivity Vary with Insular Neuronal Activity in Fibromyalgia Patients. Presented at the 2006 American College of Rheumatology.

12. Harris RE, Zubieta J-K, Scott DJ, Gracely RH, and Clauw DJ. Differential Sustained Changes in μ-Opioid Receptor (MOR) availability following Acupuncture and Sham Acupuncture Therapy in Fibromyalgia (FM). Presented to the American College of Rheumatology, 2007.
13. Harris, R., Sundgren, P., Hubbard, J., Craig, A.D., Clauw, D. (October 2009). Bilateral Anterior Insular Glutamate (Glu) is Asymmetrically Associated with Experimental Pain in Individuals with Fibromyalgia and Pain-Free Controls. Poster presented at the ACR/ARHP Annual Scientific Meeting.
14. Harris, RE. Sundgren, PC., Kirshenbaum, E., Xiang, Z., and Clauw, DJ. Variation in Glutamate and Glutamine Levels within the Anterior Insula are Associated with Changes in Anxiety and Pain in Fibromyalgia (FM). Presented to the American College of Rheumatology, 2008.
15. Harris, RE., Sundgren, PC., Pang, Y., Xiang, Z., Gracely, RH., Clauw, DJ., Variation in Glutamate and Glutamine levels within the Insula are Associated with Improvements in Clinical and Experimental pain in Fibromyalgia (FM). Presented to the American College of Rheumatology, 2007.
16. Harris, RE., Sundgren, PC., Pang, Y., Xiang, Z., Gracely, RH., Clauw, DJ., Variation in Glutamate and Glutamine Levels within the Insula are associated with Improvements in Clinical and Experimental Pain in Fibromyalgia (FM). Presented at the International Association for the Study of Pain, 2008. *(See above abstract)*
17. Harrison, R.K.,Urwin, C., Bhavsar, R., Harris, R., Clauw, D., Harte, S. (October 2009.) Comparison Between Pressure and Thermal Conditioning Stimuli in the Evaluation of Descending Noxious Inhibitory Control (DNIC) in Fibromyalgia Patients and Healthy Controls. Poster presentation at the ACR/ARHP Annual Scientific Meeting.
18. Hsu, MC, Geisser, ME, Lyden, AK, Williams, DA, Clauw, DJ (2007). Catastrophizing and Fatigue are Associated with Poorer Perceived Physical Function Relative to Objective Activity Measures in Fibromyalgia. Arthritis and Rheumatism, 56(9);S603-S603.
19. Hsu, MC, Kim, S., Sundgren, P., Pang, Y., Gracely, R., Clauw, D., Harris, R. (2007) Significant Association between Changes in Glutamate Levels and fMRI BOLD Signal in the Posterior Insula of Fibromyalgia Patients. Presented at the ACR conference in 2007.
20. Hsu, Sundgren, Harris, Fernandes, Welsh. (2008). Differences in regional gray-matter density between fibromyalgia patients and controls: A voxel-based morphometry study. Presented at the 2008 conference for the American Pain Society.
21. Ichesco, E., Bhavsar, R., Harris, R., Clauw, D., Gracely, R., Williams, D., (October 2009). Neuroimaging of Evoked Pain in Individuals with Fibromyalgia and Healthy Controls. Poster presented at the ACR/ARHP Annual Scientific Meeting.
22. Jones CW, McLean SA, Sochor MR, Newton CRH, Withrow AD, Fowler J, Stanislawski B, Williams DA, Liberzon I, Clauw DJ. (2006) Persistant Musculoskeletal Pain and Posttraumatic Stress Disorder Symptoms after Motor Vehicle Collision Share ED Symptom Risk Factors and Outcomes. Arthritis and Rheumatism, 54(9);S608-S608.
23. Lyden AK, Glass JM, Byrne-Dugan CJ, Renard BM, Gupta AK, As-Sanie S, Dadabhoy D, Williams DA, Clauw DJ. (2006). Pain and Fatigue Symptoms in Healthy Individuals after Sleep and/or Exercise Restriction. Presented at the 2006 American College of Rheumatology.
24. Lyden, A.K., Glass, J.M., Byrne-Dugan, C.J., Renard, B.M., Gupta, A.K., As-Sanie, S., Dadabhoy, D., Williams, D.A., Clauw, D.J. (November, 2006). Pain and fatigue symptoms in healthy individuals after sleep and/or exercise restriction. Poster presented at the annual meeting of the

American College of Rheumatolgy, Washington DC. *Arthritis & Rheumatism, 54, supplemental issue. (see above abstract)*

25. McLean SA, Switzer M, Jones CW, Sochor MR, Newton CRH, Withrow A, Fowler J, Williams DA, Stein PK, Liberzon I, Clauw DJ. (2006). Emergency Department Physiologic Predictors of Pain and Psychological Sequelae after Motor Vehicle Collision. Presented at the 2006 American College of Rheumatology.

26. Patel R, Clauw DJ, Gracely RH. (2005). fMRI Analysis of Innocuous Pressure in Patients with Fibromyalgia. Journal of Pain (abstract supplement), 6, 3, S27. Presented at the 24th Annual Scientific Meeting of the American Pain Society. *(not available)*

27. Patel R, Glass J, Clauw DJ, Gracely RH. (2005). Mechanisms of Task Induced Deactivation in Fibromyalgia. IASP Press (abstracts), 1259-P129, 450. Presented at the 11th World Congress on Pain of the International Association for the Study of Pain, August 21-26, 2005, Sydney, Australia, IASP Press. *(not available)*

28. Patel R, Glass J, Clauw DJ, Gracely RH. Time course of pressure task-induced deactivations in fibromyalgia and healthy controls. 52, 9, S(#118) Presented at the American College of Rheumatology 69th Annual Scientific Meeting, November 12-17, 2005, . *(not available)*

29. Patel R, Gracely RH, Naylor GA, Michalik BK, Skalski L, Clauw DJ. (2006). Altered Temporal Sequences of Evoked Brain Activity in Fibromyalgia. Presented at the 2006 American College of Rheumatology.

30. Patel R, Michalik BK, Skalski LM, Clauw DJ, Gracely RH. (2006). Stimulation Duration Alters the Initial fMRI Response to Painful Pressure in Fibromyalgia and Healthy Contols. Presented at the 2006 American College of Rheumatology.

31. Patel, R., Williams, DA, Gracely, RH, Skalski, L., Chriscinske, SJ, Alesi, G., Clauw, DJ (2007). Functional MRI (fMRI) of Pain Processing is Stable Over Time in Fibromyalgia (FM) Patients without Changes in Clinical Status. Arthritis and Rheumatism, 56(9);S92-S92.

32. Poznanski, A., Hsu, M., Gracely, RH., Clauw, DJ., and Harris, RE. Differences in Central Neural Pain Processing Following Acupuncture and Sham Acupuncture Therapy in Fibromyalgia (FM). Presented to the American Pain Society, 2008.

33. Poznanski, Ann, Integrative Medicine: When Main Stream Practice Embraces Alternative/Complementary Treatments, Fibromyalgia and Acupuncture: Clinical Research Update. Presented at the Michigan State Medical Society Annual Scientific Meeting, October 2008. *(not available)*

34. Qiu, Y. Zubieta, J-K., Scott, D., Gracely, RH., Clauw, DJ. and Harris, RE. Central μ-Opioid Receptor (MOR) Availability covaries with Mood State and Pain in Fibromyalgia (FM). Presented to the American Pain Society 2008.

35. Robinson D, McLean SA, Swor R, Zaleski EM, Mistry Y, Schon S, Sochor MR, Newton CRH, Liberzon I, Clauw DJ. Characteristics Associated with Neck Pain Persistence versus Recovery after Minor Motor Vehicle Collision. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

36. Schon S, McLean SA, Mistry Y, Zaleski EM, Swor R, Robinson D, Sochor MR, Newton CRH, Liberzon I, Clauw DJ. Predictors of Persistent Moderate or Severe Neck and/or Back Pain 1 and 6 Months after Minor Motor Vehicle Collision. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

37. Schon S, McLean SA, Zaleski EM, Swor R, Robinson D, Mistry Y, Sochor MR, Newton CRH, Liberzon I, Clauw DJ. Racial Disparity in Pain Outcomes after Minor Motor Vehicle Collision. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007. *(not available)*

38. Scott, R.E. Harris, G.A. Naylor, J.B. Romond, A.R. Bradford, R.H. Gracely, D.J. Clauw, J. Zubieta,. (2006). Increased mu-Opioid Receptor Availability is Detected During Clinical Pain Reduction in Fibromylagia Patients. Presented at the 2006 ACR/ARHP Scientific Conference.

39. Switzer M, McLean SA, Jones CW, Sochor MR, Newton CRH, Withrow AD, Fowler J, Williams DA, Liberzon I, Clauw DJ. (2006). Pre-MVC Symptoms and Psychological Characteristics are Associated with Persistent Pain and Psychological Symptoms after MVC. Arthritis and Rheumatism, 54(9);S609-S609.

40. Williams, D.A., Ambrose, K., Skalski, L., Muroff, J., Zwinck, L., Clauw, D. (October 2009). Improving Internal Locus of Pain Control in Fibromyalgia. Presented at the ACR/ARHP Annual Scientific Meeting.

41. Williams, D.A., Glass, J.M., Barjola, P., Zwinck, L., Clauw, D. (October 2009). Cognitive Dysfunction in Fibromyalgia Assessed by the Multiple Abilities Self-Report Questionnaire. Presented at the ACR/ARHP Annual Scientific Meeting.

42. Williams, DA, Patel, R., Skalski, L., Chriscinske, SJ, Rubens, M., Lapedis, J., Harris, RE, Gracely, RH, Clauw, DJ (2007). Functional MRI (fMRI) Appears to Act as a Biomarker in Fibromyalgia (FM) by Identifying Neurobiological Correlates of Changes in Pain Over Time. Arthritis and Rheumatism, 56(9);S91-S91.

43. Withrow AD, McLean SA, Sochor MR, Newton CRH, Switzer M, Fowler J, Clauw DJ, Williams DA. (2006) Cognitive and Behavioral Factors Assessed 3-7 Days after Motor Vehicle Collision are Associated with Persistant Pain and Psychological Symptoms. Arthritis and Rheumatism, 54(9);S123-S124.

44. Zaleski, E, McLean, SA, Newton, CRH, Withrow, A., Fowler, J., Williams, DA, Stein, PK, Clauw, DJ, Liberzon, I. (2007). Emergency department physiologic predictors of pain and psychological sequelae after motor vehicle collision. Biological Psychiatry, 61(8);239S-240S. *(Not available)*

7 APPENDICES

A. List of staff funded by this award
B. Screenshots of "Living Well with FM" Telehealth CD
C. Screenshots of the "KnowFibro" website
D. Copies of referenced publications
E. Copies of referenced abstracts

APPENDIX A.

Funded Personnel

Staff List

Chronic Pain and Fatigue Research Center
All staff sponsored by DoD Cooperative Agreement DAMD-17-00-2-0018

Key Personnel

Clauw, Daniel	PI and Center Director Jul 2002 – Aug 2008
Williams, David Director	Associate Center Director Behavioral /Data Handling Director Human Subjects Core Jul 2002 – Aug 2008
Gracely, Richard	Former Director Mechanistic Research Director Neural Imaging Core Jul 2002 – Oct 2004

Co-Investigators / Collaborators

Glass, Jennifer	Nov 2002 – Sep 2008
Harris, Richard E	Sep 2002 – Aug 2007
Ognenovski, Vladimir	May 2004 – Sep 2007
Kazmers, Irene	May 2004 – Nov 2004
Mc Lean, Samuel	Jul 2005 – Apr 2006
Geisser, Michael	Apr 2003 – Dec 2007
Gerstner, Geoffrey	Mar 2005 – Nov 2007
Hernandez, Luis	Dec 2004 – Aug 2007
Sen, Ananda	Oct 2004 – Sep 2007
Dadabhoy, Dina	Jul 2006 – Mar 2007
Gioia-Hasick, Deborah	Feb 2005 – Apr 2005
Kalbfleisch, John	Feb 2003 – Feb 2005

Research Staff

Ambrose, Kirsten	Jul 2002 – May 2008
Bonner, Joseph	Feb 2003 – Jun 2004
Brish, Linda	Oct 2003 – Aug 2004
Cox, Douglas	May 2004 – May 2005
Giesecke, Jutta	Jul 2002 – Oct 2003
Giesecke, Thorsten	Jul 2002 – Nov 2003
Grant, Masilo	Sep 2002 – Sep 2003
Groner, Kimberly	Jul 2002 – Apr 2007
Henschell, Joshua	Apr 2003 – Nov 2003
Jack, Christy	Jun 2003 – Sep 2003
Leone,Virginia	Aug 2002 – May 2009
Lyden, Angela	Jul 2002 – Mar 2008
Mannerkorpi, Kaisa	Aug 2002 – Feb 2003
Michalik, Brian	Jun 2004 – Dec 2006
Olivadoti, Melissa	Sep 2002 – Nov 2005
Perelman, Cynthia	Jun 2003 – Aug 2003
Snorrason, Rhonda	Nov 2003 – May 2004

Taylor-Moon, Denise	Sep 2002 – Dec 2006
King, Anthony	Sep 2003 – Jul 2005
Miner, Jennifer	Apr 2005 – Feb 2008
Chriscinske, Samantha	Sep 2003 – Mar 2006
Friedman, Daniel	Oct 2003 – Oct 2004
Klykylo, Katherine	Aug 2005 – Mar 2007
Mayo-Bond, Laura	Jul 2004 – Oct 2007
Naylor, Greta	Dec 2004 – Jul 2006
Patrick, Barbara	Jul 2003 – Jul 2005
Romond, John	Sep 2005 – Apr 2006
Skalski, Linda	Sep 2005 – Nov 2007
Zwinck, Lynn	Dec 2008 – Jul 2009

Professional/Administrative Staff

Bartold, Joanna	Nov 2002 – Dec 2003
Brown, Scott	Sep 2002 – Mar 2003
Brummett, Katherine	Dec 2008 – Apr 2009
Curtis, Christopher	Jun 2004 – Apr 2005
Krishnan, Sumati	Feb 2005 – Mar 2008
Manoharan,	Nov 2004 – Mar 2006
Muroff, Jordana	Dec 2003 – Jun 2006
Palrecha, Neel	Jul 2004 – Nov 2004
Parkanzky, Paul	May 2004 – Nov 2004
Renard, Brian	Feb 2004 –Sep 2005
Roosevelt, Vickie	Sep 2002 – Oct 2003
Segar, Michelle	May 2003 – Sep 2005
Silverthorn, Renee	Dec 2004 – Jan 2007
Sprey, Sherri	Feb 2003 – Jun 2008
Willey, Mike	Feb 2006 – Feb 2008
Zolikoff, Mikhail	Dec 2002 – Jun 2003

Other Support Personnel

Torgersen, John	Form G Employees	Oct 2004 – Jun 2006
Biswas, Pinaki	GSRA	Feb 2003 – Sep 2007
Byrne-Dugan, Cathryn	GSRA	Oct 2005 – Feb 2007
Brucksch, Christine	MNA Nurse	Feb 2003 – Oct 2004
Hogue, Ruby	Office (Temporary)	Oct 2004 – Nov 2004
Maleki Masouleh, Mehrnaz	Service Staff (Temporary)	Oct 2003 – Sep 2005

<u>Collaborating Researchers</u> (not funded)

University of Michigan ** No longer at University of Michigan*

* Leslie Crofford, M.D.	Co-investigator
Kenneth Casey, MD	Co-investigator
John Wiley, M.D.	Co-investigator
* Scott Brown, Ph.D.	Co-investigator
* Thorsten Giesecke, M.D.	Co-investigator
* Jutta Giesecke, M.D.	Co-investigator
Christian Stohler, D.D.S.	Co-investigator

Jon-Kar Zubieta, M.D., Ph.D.	Co-investigator
Jack Kalbfleisch, Ph.D.	Co-investigator, Biostatistics
Pia Sundgren, M.D.	Co-investigator, SLE functional imaging study
* Kayode Williams, M.D.	Co-investigator, Pain outcomes study
Irene Kazmers, M.D.	Co-Medical Monitor
Vladimir Ognenovski, M.D.	Co-Medical Monitor

Georgetown University

Meredith Cary, PsyD.	Clinical Psychologist
Samantha Smith, Ph.D.	Clinical Psychologist
James Baraniuk, M.D.	Director, Bioassay Core
Gail Whalen, B.S.	Lab Manager
David Cafaro Com	puter Engineer

Avera-McKennan Research Institute

Dave Kapaska, M.D.	Medical Monitor
Dave Kuper, Ph.D.	Executive Director

USUHS

Thomas Balkin, Ph.D.	Co-investigator
Gary Kamimori, Ph.D.	Co-investigator
Willem Kop, Ph.D.	Co-investigator
Charles Engel, M.D.	Co-investigator

Wash. U./Barnes

Phyllis Stein, Ph.D.	Consultant, Heart rate variability

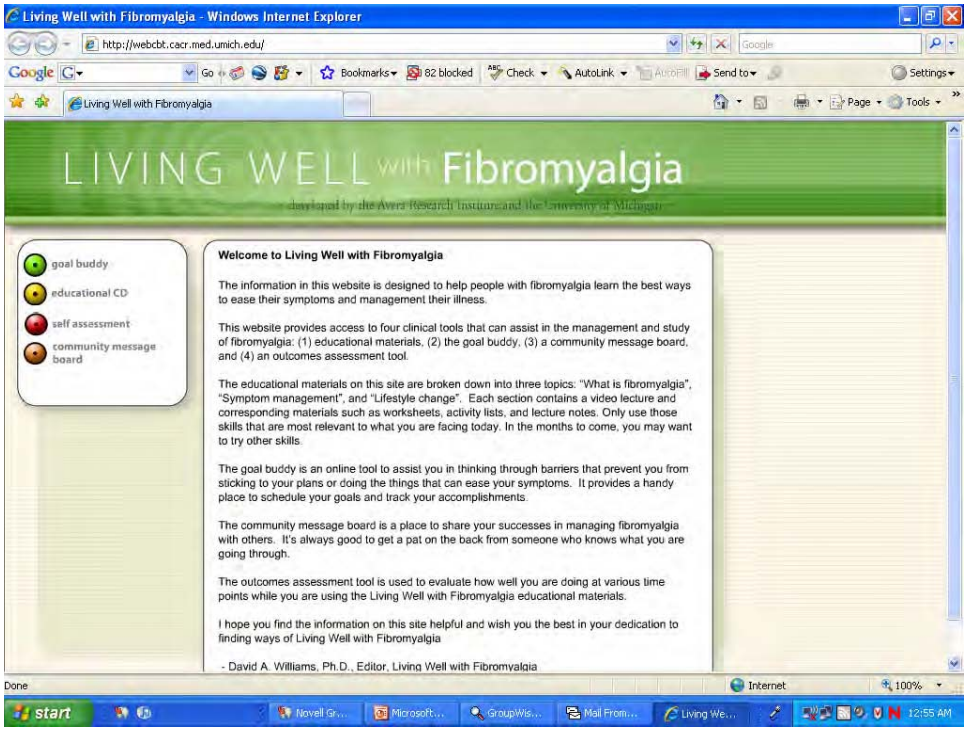
Indiana University

James Skinner, Ph.D.	Consultant, Exercise
Neal Oldridge, Ph.D.	Consultant, Exercise

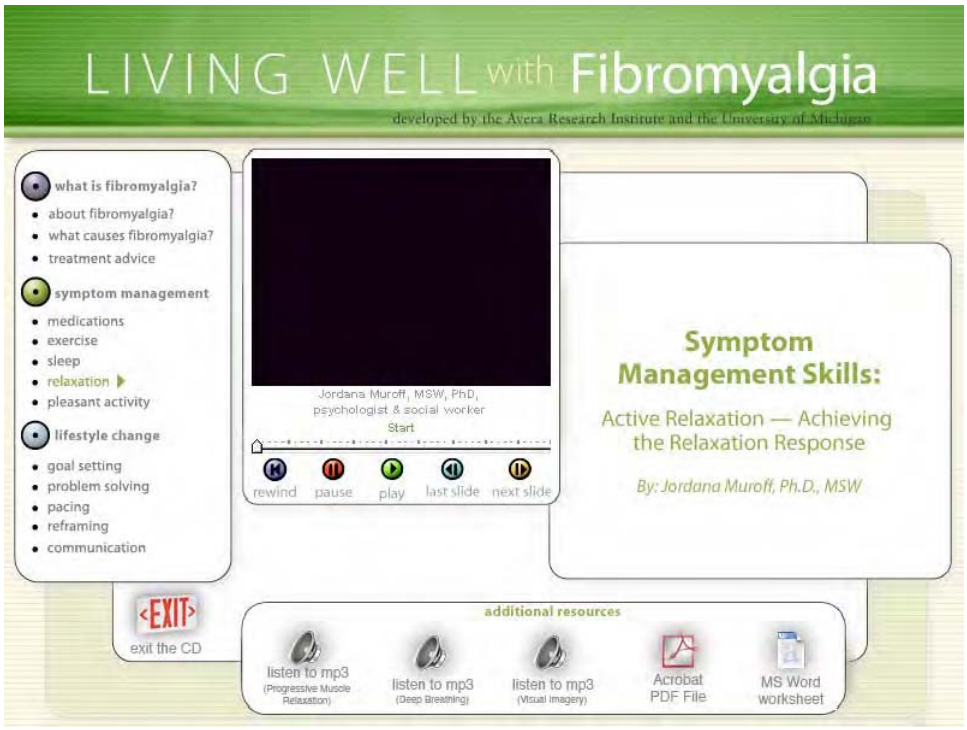
Screenshots

Living Well with Fibromyalgia CD

Internet and Telehealth Enhanced CBT
for the Management of Fibromyalgia


Living Well with Fibromyalgia - Windows Internet Explorer
http://webcbt.cacr.med.umich.edu/
Living Well with Fibromyalgia
LIVING WELL with Fibromyalgia
developed by the Avera Research Institute and the University of Michigan
goal buddy
educational CD
self assessment
community message board
Welcome to Living Well with Fibromyalgia
The information in this website is designed to help people with fibromyalgia learn the best ways to ease their symptoms and management their illness.
This website provides access to four clinical tools that can assist in the management and study of fibromyalgia: (1) educational materials, (2) the goal buddy, (3) a community message board, and (4) an outcomes assessment tool.
The educational materials on this site are broken down into three topics: "What is fibromyalgia", "Symptom management", and "Lifestyle change". Each section contains a video lecture and corresponding materials such as worksheets, activity lists, and lecture notes. Only use those skills that are most relevant to what you are facing today. In the months to come, you may want to try other skills.
The goal buddy is an online tool to assist you in thinking through barriers that prevent you from sticking to your plans or doing the things that can ease your symptoms. It provides a handy place to schedule your goals and track your accomplishments.
The community message board is a place to share your successes in managing fibromyalgia with others. It's always good to get a pat on the back from someone who knows what you are going through.
The outcomes assessment tool is used to evaluate how well you are doing at various time points while you are using the Living Well with Fibromyalgia educational materials.
I hope you find the information on this site helpful and wish you the best in your dedication to finding ways of Living Well with Fibromyalgia
- David A. Williams, Ph.D., Editor, Living Well with Fibromyalgia
Done
Internet
100%
start
12:55 AM


LIVING WELL with Fibromyalgia
developed by the Avera Research Institute and the University of Michigan
what is fibromyalgia?
about fibromyalgia?
what causes fibromyalgia?
treatment advice
symptom management
medications
exercise
sleep
relaxation
pleasant activity
lifestyle change
goal setting
problem solving
pacing
reframing
communication
What Is Fibromyalgia?
EXIT
exit the CD
Daniel Clauw, MD, rheumatologist
Start
rewind
pause
play
last slide
next slide


LIVING WELL with Fibromyalgia
developed by the Avera Research Institute and the University of Michigan
what is fibromyalgia?
about fibromyalgia?
what causes fibromyalgia?
treatment advice
symptom management
medications
exercise
sleep
relaxation
pleasant activity
lifestyle change
goal setting
problem solving
pacing
reframing
communication
Jordana Muroff, MSW, PhD,
psychologist & social worker
Start
rewind
pause
play
last slide
next slide
Symptom Management Skills:
Active Relaxation — Achieving the Relaxation Response
By: Jordana Muroff, Ph.D., MSW
EXIT
exit the CD
additional resources
listen to mp3
(Progressive Muscle Relaxation)
listen to mp3
(Deep Breathing)
listen to mp3
(Visual Imagery)
Acrobat PDF File
MS Word worksheet

Screenshots

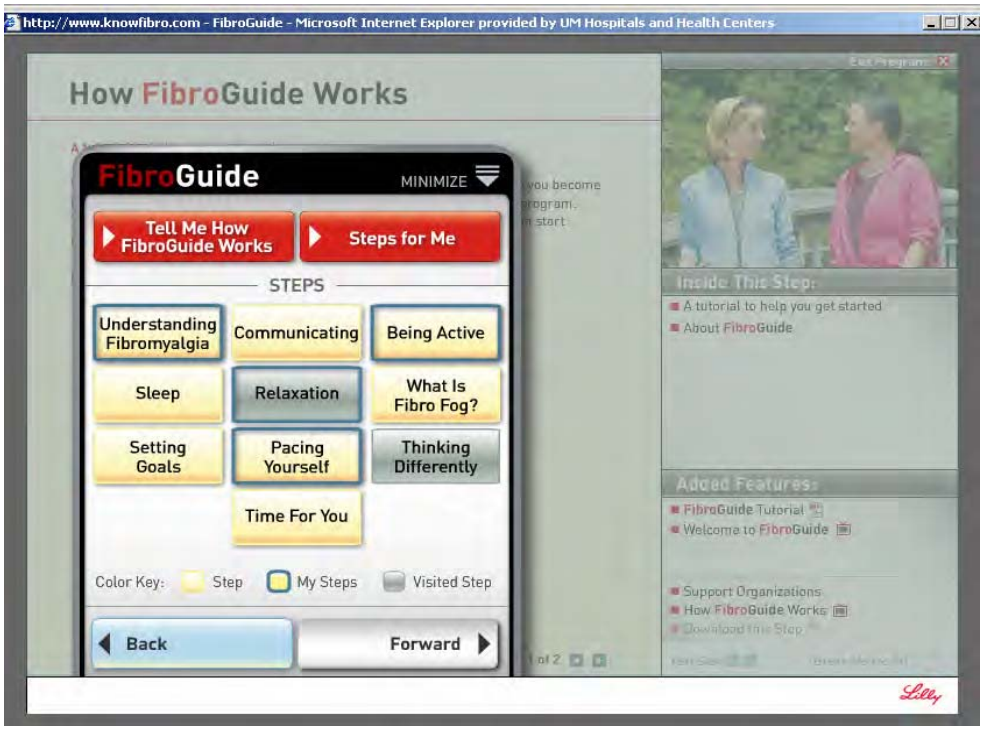
Know Fibro and Fibro Guide

www.knowfibro.com

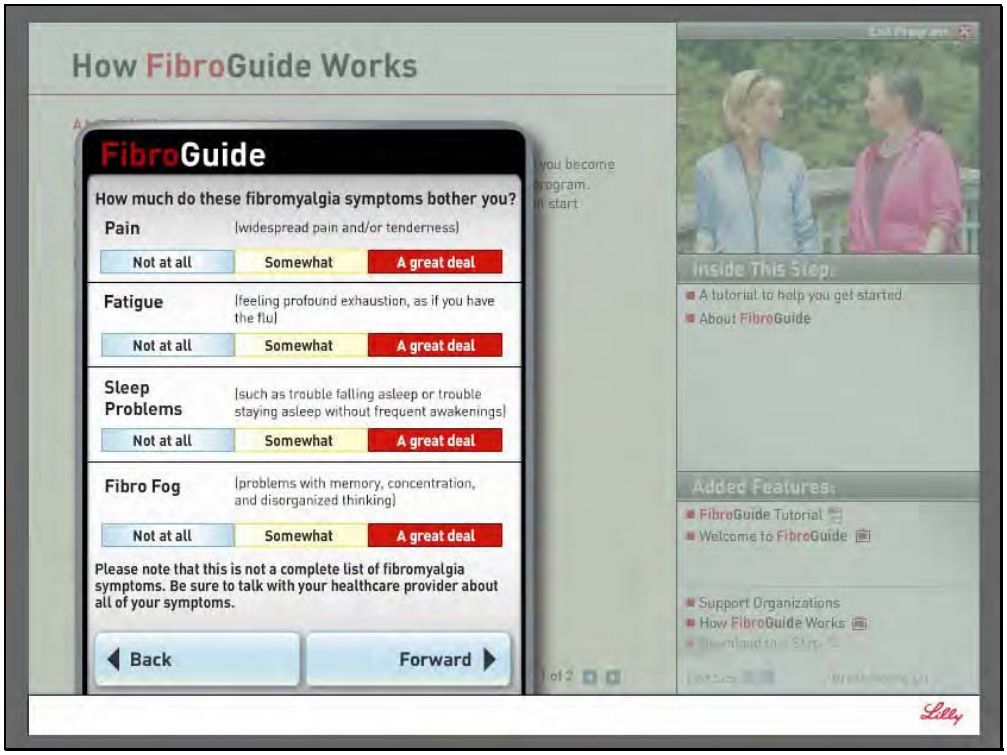
Introduction to Know Fibro main page:

Introduction to the Interactive Fibro Guide:

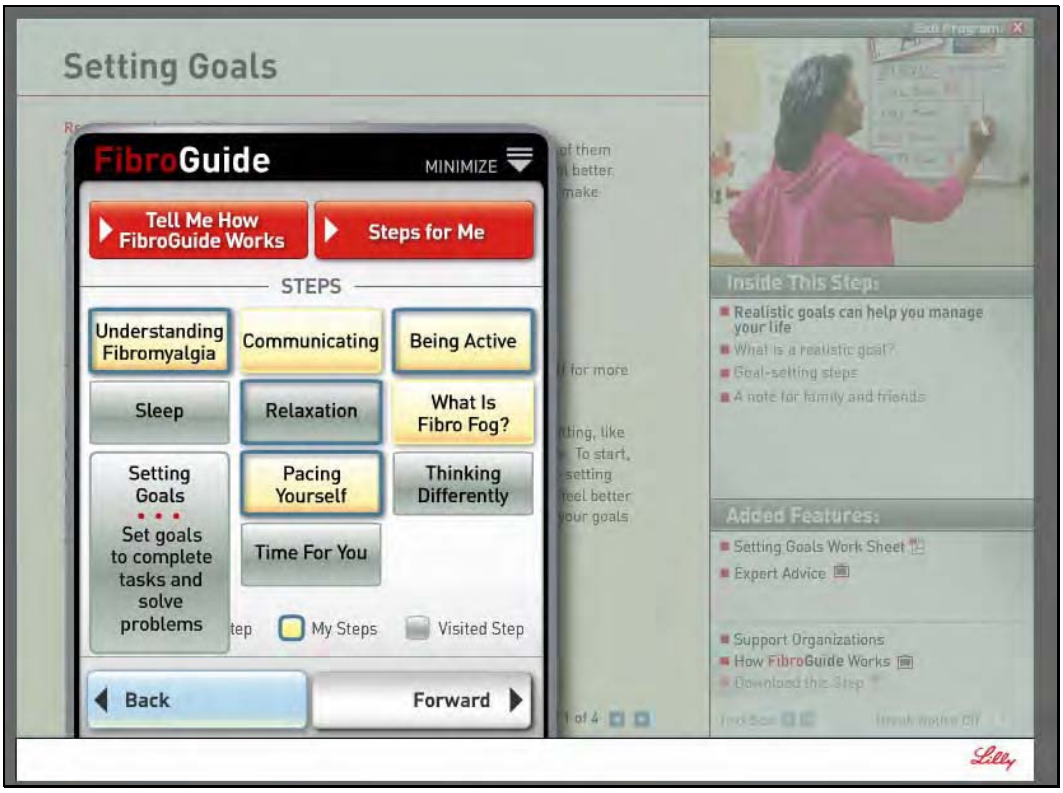
Customize Fibro Guide for specific symptoms:

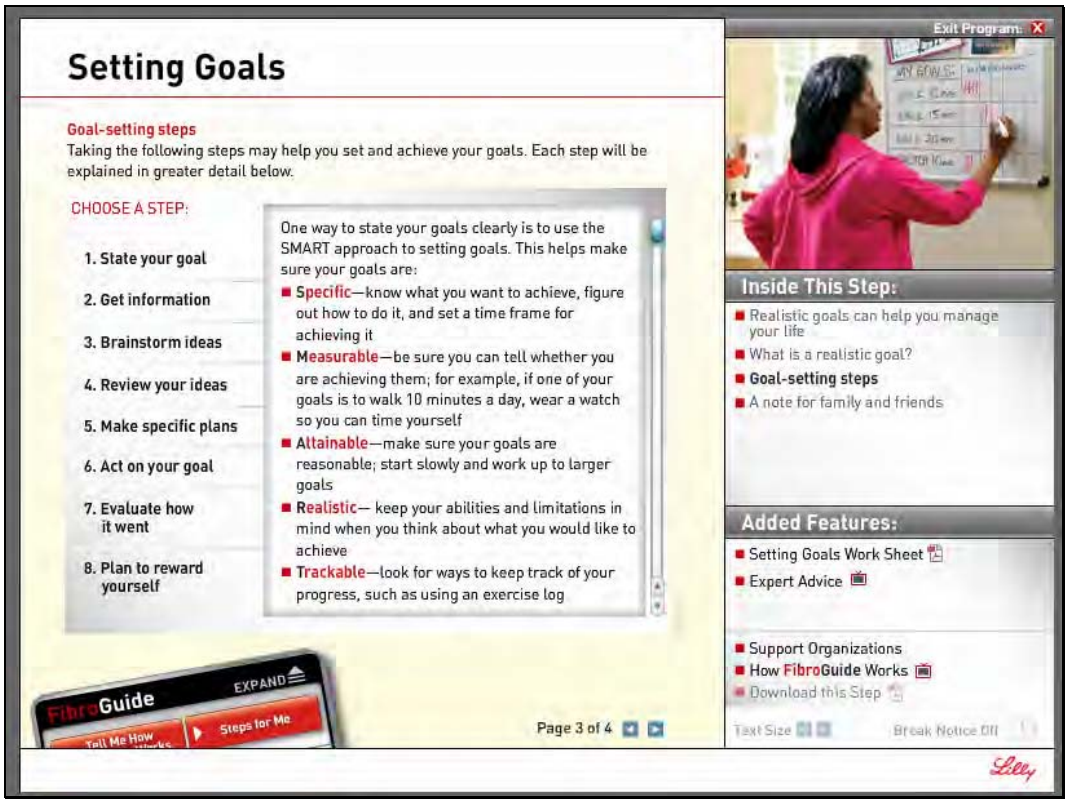


Responses identify most applicable virtual modules:



Select modules and adopt suggested strategies:





APPENDIX D.

Referenced Journal Articles

Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pain 11 (2007) 202–207
www.EuropeanJournalPain.com

The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome

Michael E. Geisser [a,b,*], Richard H. Gracely [a], Thorsten Giesecke [c], Frank W. Petzke [c], David A. Williams [a], Daniel J. Clauw [a]

[a] *Chronic Pain and Fatigue Research Center, Department of Internal Medicine, Division of Rheumatology, University of Michigan, Ann Arbor, MI, United States*
[b] *Department of Physical Medicine and Rehabilitation, University of Michigan Health System, 325 E. Eisenhower Parkway, Ann Arbor, MI 48108, United States*
[c] *Department of Anesthesiology and Intensive Care, University of Cologne, Cologne, Germany*

Received 5 October 2005; received in revised form 30 January 2006; accepted 5 February 2006
Available online 20 March 2006

Abstract

Evoked or experimental pain is often used as a model for the study of clinical pain, yet there are little data regarding the relationship between the two. In addition, there are few data regarding the types of stimuli and stimulus intensities that are most closely related to clinical pain.

In this study, 36 subjects with fibromyalgia (FM), chronic fatigue syndrome (CFS), or both syndromes were administered measures of clinical pain and underwent a dolorimetry evaluation. Subjects also underwent experimental pain testing utilizing heat and pressure stimulation. Stimulation levels evoking low, moderate and high sensory intensity, and comparable levels of unpleasantness, were determined for both types of stimuli using random staircase methods. Clinical pain was assessed using visual analogue ratings and the short form of the McGill Pain Questionnaire (MPQ).

Ratings of heat pain sensation were not significantly associated with clinical pain ratings, with the exception of unpleasantness ratings at high stimulus intensities. Pain threshold and tolerance as assessed by dolorimetry were significantly associated with average measures of clinical pain. Both intensity and unpleasantness ratings of pressure delivered using random staircase methods were significantly associated with clinical pain at low, moderate and high levels, and the strength of the association was greater at increasingly noxious stimulus intensities.

These findings suggest that random pressure stimulation as an experimental pain model in these populations more closely reflects the clinical pain for these conditions. These findings merit consideration when designing experimental studies of clinical pain associated with FM and CFS.

Keywords: Fibromyalgia; Chronic fatigue syndrome; Chronic pain; Experimental pain

1. Introduction

Experimental studies designed to deliver noxious stimuli to subjects under controlled conditions are frequently used to make inferences about clinical pain conditions. Despite this, little is known about the

* Corresponding author. Tel.: +1 734 763 6501; fax: +1 734 936 7048.
E-mail address: mgeisser@med.umich.edu (M.E. Geisser).

1090-3801/$32
doi:10.1016/j.ejpain.2006.02.001

relationship between experimental pain perception and clinical pain, and there is a lack of research on the experimental methods and types of stimuli that are most highly associated with clinical pain (Gracely, 1999). Such studies are highly important as evoked pain is increasingly being used to study central nervous system (CNS) abnormalities associated with clinical pain conditions such as fibromyalgia (FM), temporomandibular disorders, vulvodynia, and other entities (Geisser et al., 2003; Giesecke et al., 2004; Diatchenko et al., 2005; Petzke et al., 2003a). While pain is not a central feature of chronic fatigue syndrome (CFS), five of eight minor criteria (of which four are necessary to make the diagnosis) for CFS are pain-based (Fukuda et al., 1994). Common CNS abnormalities have been proposed to underlie all of these disorders (Clauw and Chrousos, 1997), and determining the experimental methods that best reproduce the clinical abnormalities associated with these conditions is crucial to their study.

Previous research has shown that persons with FM display heightened responsiveness to auditory tones (McDermid et al., 1996), contact thermal heat in both the noxious and innocuous ranges (Geisser et al., 2003; Kosek et al., 1996; Kosek and Hansson, 1997; Lautenbacher et al., 1994; Staud et al., 2001), ischemic pain (Kosek and Hansson, 1997), pressure applied to the thumb (Gracely et al., 2002; Petzke et al., 2003a) and electrical stimulation (Lautenbacher et al., 1994). Differences between FM subjects and controls have also been observed using methodologies that stimulate abnormal temporal summation of pain or wind-up (Staud et al., 2001, 2003) and the regulation of diffuse noxious inhibitory controls (Kosek and Hansson, 1997). However, only a few studies have examined how these abnormalities relate to the experience of clinical pain. Lautenbacher et al. (1994) reported low associations between measures of clinical pain and responses to electrocutaneous stimuli, pressure and heat. The authors also found that pressure pain thresholds at two sites were significantly associated with clinical pain. Staud et al. (2003) found that a combination of variables including measures of wind-up, pain-related negative affect, and tender point counts accounted for 49% of the variance in clinical pain. Further research is needed to determine the types of stimuli and experimental methods that are most highly associated with clinical pain states. In addition, previous research suggests that experimental methods that employ gradually ascending stimulation are more highly associated with psychological factors that may bias pain ratings (Petzke et al., 2003).

In the present study, we examined the relationships between clinical pain and a variety of evoked pain measures including gradually ascending pressure (dolorimetry) and a random staircase method of stimulus presentation of both pressure and heat stimuli. Based on prior research, we hypothesized that the random staircase methods would be more highly associated with measures of clinical pain compared to dolorimetry. In addition, we hypothesized that pressure pain perception would be more highly associated with measures of clinical pain compared to heat pain perception, as previous research has suggested that pressure sensitivity is highly associated with musculoskeletal pain syndromes (Diatchenko et al., 2005; Rollman and Lautenbacher, 2001). Since both momentary and average clinical pain were assessed, we also examined whether evoked pain was more highly associated with patients' usual pain, or more highly correlated with pain at the time of testing.

2. Materials and methods

2.1. Subjects

Thirty-six subjects who met either the 1990 American College of Rheumatology criteria for fibromyalgia (FM) (Wolfe et al., 1990), the diagnostic criteria for chronic fatigue syndrome (CFS) (Fukuda et al., 1994), or both diagnoses, were included in the study. Subjects with CFS had to have at least one pain symptom to be eligible. Eight subjects were diagnosed with FM alone, eight with CFS alone, and 20 fulfilled the diagnostic criteria for both disorders. Twenty-seven were female, and nine were male. Twenty-three were Caucasian, six were African-American, two were Hispanic, two were Asian-American, and three were of other descent. The mean age was 39.6 (SD = 9.2) years. Mean duration of pain was 96.5 months (SD = 80.9). Subjects with psychiatric disorders that did not interfere with study participation were not excluded.

The study was approved by the Georgetown University Medical Center's institutional review board, and informed consent was obtained from all participants for study on the General Clinical Research Center. All patients underwent a comprehensive screening during which the diagnosis was confirmed and co-morbidities were evaluated. Exclusion criteria were severe physical impairment, medical conditions that were capable of causing patients' symptoms (e.g., morbid obesity, autoimmune/inflammatory diseases, cardiopulmonary disorders), uncontrolled endocrine or allergic disorders (i.e., hyper-/hypothyroidism, diabetes, allergic rhinitis), malignancy, severe psychiatric illnesses (e.g., schizophrenia, substance abuse), factors known to affect the hypothalamic pituitary axis (HPA) or autonomic function (e.g., cigarette smoking, daily intake of caffeine exceeding the equivalence of two cups of coffee), or medication usage other than as-needed analgesics (excluding long-term narcotics). We did not exclude subjects with psychiatric conditions that are associated with HPA dysfunction (e.g., major depression). Eleven subjects who fulfilled the diagnostic criteria were excluded as

these subjects did not complete all of the study measures examined in the current manuscript.

Subjects who qualified for inclusion in the study were scheduled for a 2-day study protocol. They were asked to discontinue intake of antidepressants up to four weeks ahead of the appointment (depending on the drug), but were allowed to use non-steroidal anti-inflammatory drugs until three days before the appointment. On the first day of the study, patients completed the self-report questionnaires and were familiarized with the pain testing paradigm. On the following day, they participated in a pain psychophysical testing session.

2.2. Measures

2.2.1. Clinical pain

Clinical pain was assessed using the short-form of the McGill Pain Questionnaire (MPQ; Melzack, 1987). This questionnaire contains 15 pain adjectives, and a total score is obtained by summing responses to all the items. The present pain intensity (PPI) subscale was examined as an indicator of pain intensity at the time of testing. The scale is sensitive to change produced by various pain interventions, and is highly correlated with the parent scale (Melzack, 1987).

Self-report of clinical pain intensity was also obtained by visual analogue scale (VAS) ratings. The scale was 100 mm long and anchored by the statements "no pain" on the left and "the most intense pain imaginable" on the right. Separate VAS scales were used to measure subjects' level of pain on the day of testing and average pain over the past month. VAS ratings have demonstrated good reliability (Boeckstyns and Backer, 1989; Revill et al., 1976) and concurrent validity when compared to other methods of pain measurement (Downie et al., 1978; Jensen et al., 1989).

2.2.2. Pressure and heat pain assessment

Evoked pain was assessed for both pressure and heat stimuli. Pressure pain sensitivity was evaluated by subjective scaling of pain sensations evoked by discrete 5-s pressure stimuli applied to the fixated left thumbnail with a 1-cm^2 hard rubber probe. Previous studies have shown that "neutral" regions, such as the thumb, accurately reflect an individual's overall pressure pain sensitivity (Petzke et al., 2001). The rubber probe was attached to a hydraulic piston, which was connected via a combination of valves to a second piston. Application of calibrated weights to the second piston produced controlled, repeatable pressure pain stimuli of rectangular waveform, that is, subjects experienced no pressure, then the target stimulus pressure when the appropriate weight was placed on the second piston. Subjects rated the intensity and unpleasantness dimensions of pressure pain sensations using a combined numerical (0–20) analog descriptor scale (Gracely et al., 1979). For each dimension, a series of 5-s stimuli were delivered to the right thumbnail in ascending order in 0.5 kg of force per square centimeter (kg/cm^2) increments after an initial stimulus of 0.25 kg/cm^2, up to a maximum of 10 kg/cm^2. A second series of pressure stimuli was administered using the multiple random staircase (MRS) method (Gracely et al., 1988). A software system uses the data collected from the ascending series to compute starting stimulus intensities for another set of stimuli controlled by the method of MRS's. The MRS is an interactive system in which the software logic continuously adjusts the stimulus intensity to maintain ratings at several specific levels. In this implementation, three independent staircases are titrated to produce pain sensations rated between 0 and 1 (no sensation to faint pain), between 9 and 10 (mild–moderate pain), and between 13 and 14 (strong–slightly intense pain) on the 0–20 box scale. In the remainder of this report, these levels are referred to as low, medium, and high. On each trial, the method randomly selects a staircase and delivers the stimulus intensity associated with that staircase. The response determines the next stimulus delivered by that staircase the next time it is selected. This determination is based on the previous response history and uses a dynamically changing step size to estimate the stimulus intensity required to produce the level of pain associated with each particular staircase. The method will deliver 12 stimuli for each of the three staircases, for a total of 36 stimuli delivered over 12 min. If any staircase has not converged after 12 stimuli, the operator will be able to continue the method until convergence is reached or until 72 total stimuli have been delivered.

Heat pain sensations were evoked by a 1 cm diameter contact thermode system. A low-mass electrical heater on a water-perfused cold sink with feedback circuitry delivered precise stimulus waveforms with a ramp rate of 10 °C/s. The thermal stimuli were delivered to the volar surface of the non-IV forearm. As with the pressure testing, both an ascending and a multiple random staircase series of thermal stimuli were presented to each subject. The temperatures required to evoke ratings of low, medium, and high pain intensity and unpleasantness were calculated for each subject.

2.2.3. Dolorimetry

A dolorimeter with a 1 cm^2 tip was used to determine pain threshold and tolerance levels bilaterally at the thumb and lateral epicondyle. Pressure was increased at a rate of 1 kg/cm^2 per second and subjects were instructed to indicate when they first perceived pain (threshold) and when the pain became unbearable (tolerance). Pressure was stopped once the pain became unbearable or if 12 kg/cm^2 of pressure was reached. These sites were chosen as previous research has shown that these points are highly correlated with overall tenderness (Petzke et al., 2001). The measures from each

side of the body were averaged to produce one value for each stimulus site.

3. Results

Table 1 shows the means and standard deviations for pressure and thermal intensities needed to evoke sensations of mild, medium, and high sensory intensity and unpleasantness using the random staircase procedure, and displays the threshold and tolerance averages for dolorimetry measured at the thumb and lateral epicondyle.

An initial analysis examined whether the patient groups differed on any of the clinical or experimental pain measures. Oneway analysis of variance (ANOVA) revealed that the groups significantly differed on VAS ratings of pain today ($F = 7.0$, $p = .003$) and pain over the past month ($F = 4.1$, $p = .03$). Post hoc tests (Duncan) indicated that subjects diagnosed with both FM and CFS had higher ratings of pain today compared to the other two groups, and had higher VAS ratings of pain over the past month compared to subjects diagnosed with CFS alone. In addition, the groups significantly differed on pain threshold ($F = 3.2$, $p = .05$) and tolerance ($F = 3.2$, $p = .05$) assessed by dolorimetry at the lateral epicondyle. Post hoc tests revealed that subjects with CFS alone had significantly higher pain threshold and tolerances compared to subjects with both CFS and FM.

Correlations between the clinical pain measures, dolorimetry, and heat and pressure pain measures (stimulus intensities needed to evoke different levels of pain sensation) are presented in Table 2. The correlations indicate that pressure stimuli delivered using the random staircase method were significantly associated with ratings on the MPQ for both unpleasantness and intensity at all stimulus levels, with the exception of low unpleasantness ratings. In addition, pressure stimuli at high levels of intensity and unpleasantness were significantly associated with VAS ratings of pain over the past month. The magnitude of this association became greater as the stimulus intensity increased. Measures of pain threshold and tolerance assessed by dolorimetry at the lateral epicondle were significantly and inversely related to the MPQ total score and average VAS over the past month, indicating lower pain thresholds and tolerance were significantly associated with higher clinical pain. Pain thresholds and tolerances measured at the thumb using dolorimetry were not significantly associated with these same measures. None of the dolorimetry, heat or pressure pain measures were significantly correlated with measures of pain assessed on the day of testing.

Measures of heat pain sensitivity delivered using the random staircase procedure were not significantly associated with clinical pain ratings, with the exception of high unpleasantness ratings and McGill total pain scores and VAS ratings of pain over the past month.

To determine whether the significant correlations obtained between the experimental and clinical pain measures significantly differed across experimental methods, the formula for comparing two correlation coefficients from related samples was utilized (Weinberg and Goldberg, 1979, p. 412). Comparing the associations between intensity and unpleasantness levels and clinical pain assessed by the MPQ utilizing the MRS pressure method versus heat, the associations with

Table 1
Means (SD) of experimental heat and pressure measures

Measure	Mean (SD)
Lateral epicondyle threshold (kg/cm^2)	5.4 (2.5)
Lateral epicondyle tolerance (kg/cm^2)	7.2 (3.0)
Thumb threshold (kg/cm^2)	6.6 (3.0)
Thumb tolerance (kg/cm^2)	8.2 (3.1)
Low pressure intensity (kg/cm^2)	2.3 (1.8)
Medium pressure intensity (kg/cm^2)	4.7 (2.5)
High pressure intensity (kg/cm^2)	6.5 (2.7)
Low pressure unpleasantness (kg/cm^2)	2.7 (2.3)
Medium pressure unpleasantness (kg/cm^2)	5.4 (2.7)
High pressure unpleasantness (kg/cm^2)	7.4 (2.9)
Low heat intensity (°C)	38.3 (2.8)
Medium heat intensity (°C)	43.0 (4.1)
High heat intensity (°C)	46.9 (4.5)
Low heat unpleasantness (°C)	39.3 (3.6)
Medium heat unpleasantness (°C)	44.9 (4.8)
High heat unpleasantness (°C)	48.2 (4.5)

Table 2
Correlations between experimental and clinical pain measures

Measure	McGill total	VAS past month	PPI	VAS today
Dolorimeter				
Lateral epicondyle threshold	−.36*	−.34*	−.17	−.23
Lateral epicondyle tolerance	−.41*	−.35*	−.24	−.30
Thumb threshold	−.22	−.16	−.09	−.11
Thumb tolerance	−.31	−.25	−.20	−.24
Pressure				
Low intensity	−.42*	−.21	−.18	−.23
Medium intensity	−.48*	−.23	−.22	−.24
High intensity	−.52*	−.33*	−.27	−.27
Low unpleasantness	−.30	.00	−.13	−.10
Medium unpleasantness	−.45*	−.19	−.22	−.16
High unpleasantness	−.52*	−.35*	−.27	−.22
Heat				
Low intensity	−.14	−.18	.06	−.11
Medium intensity	−.20	−.31	.02	−.17
High intensity	−.24	−.31	−.03	−.15
Low unpleasantness	−.10	−.07	.03	.00
Medium unpleasantness	−.20	−.24	.01	−.08
High unpleasantness	−.36*	−.35*	−.15	−.17

* $p < .05$.

MRS pressure were significantly higher for the medium ($t = -2.3$, $p = .03$) and high ($t = -2.8$, $p = .01$) intensity stimuli compared to the same levels obtained using MRS heat. A similar result was also obtained for medium ($t = -2.1$, $p = .05$) unpleasantness stimuli. When VAS ratings of pain during the past month were examined, the associations between this measure and stimulation levels obtained using MRS heat and MRS pressure did not differ. The correlations between dolorimetry and clinical pain did not significantly differ from those observed between MRS heat or pressure and clinical pain. The magnitude of the associations between MRS pressure and clinical pain, and dolorimetry and clinical pain, were also not significantly different.

As trends were evident suggesting that higher stimulation levels were more strongly associated with clinical pain compared to less intense levels, these correlations were also compared using the same method noted above. For dolorimetry, associations between dolorimetry and clinical pain comparing the threshold and tolerance measures did not significantly differ. For MRS pressure and heat, the associations across different intensity rating levels also were not significantly different. For unpleasantness ratings, the association between pressure high unpleasantness and VAS ratings of pain over the past month was significantly greater than the association between pressure low unpleasantness and this same measure of clinical pain ($t = -2.8$, $p = .01$). Also, the difference in the associations between pressure low unpleasantness and MPQ scores and high pressure unpleasantness and MPQ scores approached significance ($t - 1.8$, $p = .08$).

4. Discussion

Pain sensitivity determined by pressure stimulation using the multiple random staircase (MRS) procedure was significantly and inversely associated with average measures of clinical pain intensity, while heat was not. Comparing the magnitude of the associations, the correlations between MRS measures of pressure and clinical pain as assessed by the MPQ were significantly higher than those obtained between MRS heat and clinical pain. None of the experimental pain measures were significantly associated with measures of clinical pain assessed at the time of testing. These findings suggest that responses to evoked pressure pain in patients with FM and CFS can be generalized to patients' overall clinical condition, and that fluctuations in clinical pain that may occur during psychophysical testing do not significantly influence evoked pain responses. These findings also suggest that pressure stimulation as an experimental pain model among subjects with FM and CFS more closely reflects the average clinical pain associated with these conditions, and is consistent with other research suggesting that mechanical stimulation is an especially sensitive measure for the analysis of pathology associated with musculoskeletal pain (Diatchenko et al., 2005; Rollman and Lautenbacher, 2001).

In general, ratings given to higher stimulus intensities were more strongly associated with average ratings of clinical pain. These findings highlight the importance of evoked pain studies and provide further justification for the use of suprathreshold stimuli in experimental pain paradigms. The findings also suggest that experimental application of innocuous stimuli as a model for clinical pain may not be as generalizable to clinical pain conditions. In addition, the findings suggest that methods used to assess pain thresholds may not be as generalizable to clinical pain compared to studies employing suprathreshold methods of pain stimulation. This conclusion needs to be interpreted cautiously as significantly higher correlations between higher levels of experimental pain stimulation and clinical pain were only obtained for unpleasantness ratings and not intensity ratings, and this finding was only evident using the MRS pressure stimulation method. Further research examining the risk/benefit of noxious stimulus intensities in relation to the generalizability of the findings and subject burden would be beneficial.

Pressure stimulation using both dolorimetry and random staircase methods were both significantly associated with average measures of clinical pain. However, our previous research suggests that random staircase methods are less prone to biases associated with gradually ascending stimuli, and therefore are less likely to be influenced by affective states that frequently accompany pain, such as depression. In the present study, the magnitude of the associations between random staircase measures of pressure sensation and clinical pain as assessed by the McGill were somewhat higher than they were for dolorimetry, although this difference was not statistically significant. Further research is needed to determine the types of evoked pain models that most closely reflect the mechanisms underlying different clinical pain conditions.

It should be noted that the design of the present study is cross-sectional, and therefore no inferences can be made about causality. In addition, this study only examined a few of the experimental pain paradigms published in the literature, and therefore the findings cannot speak to the generalizability of other experimental methods to clinical pain, such as electrical stimulation. Third, the study examined patients with pain associated with FM and CFS, and the findings may not be generalizable to other clinical pain conditions. Fourth, this study examined the correlation between clinical pain intensity and experimental pain perception, and did not examine the ability of experimental methods to discriminate between persons with and without chronic pain. Such a comparison would also be beneficial in examining the validity of various methods of experimental pain.

Acknowledgements

Funding for this study came in part from Department of the Army Grant DAMD-17002-0018 and Grant M01 RR-13297 from the National Center for Research Resources, National Institutes of Health.

References

Boeckstyns MEH, Backer M. Reliability and validity of the evaluation of pain in patients with total knee replacement. Pain 1989;38:29–33.

Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes:overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 1997;4:134–53.

Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, Belfer I, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Human Molecular Genetics 2005;14:135–43.

Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. Ann Rheum Dis 1978;37:378–81.

Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A The International Chronic Fatigue Syndrome Study Group. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994;121:953–9.

Geisser ME, Casey KL, Brucksch CB, Ribbens CM, Appleton BB, Crofford LJ. Perception of noxious and innocuous heat stimulation among healthy women and women with fibromyalgia:association with mood, somatic focus, and catastrophizing. Pain 2003;102:243–50.

Giesecke J, Reed BD, Haefner HK, Giesecke T, Clauw DJ, Gracely RH. Quantitative sensory testing in vulvodynia patients and increased peripheral pressure pain sensitivity. Obstetrics & Gynecology 2004;104:126–33.

Gracely RH. Studies of pain in human subjects. In: Wall PD, Melzack R, editors. Textbook of pain. New York: Churchill Livingstone; 1999. p. 385–407.

Gracely RH, Dubner R, McGrath PA. Narcotic analgesia: fentanyl reduces the intensity but not the unpleasantness of painful tooth pulp sensations. Science 1979;203:1261–3.

Gracely RH, Lota L, Walter DJ, Dubner R. A multiple random staircase method of psychophysical pain assessment. Pain 1988;32:55–63.

Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46:1333–43.

Jensen MP, Karoly P, O'Riordan EF, Bland Jr F, Burns RS. The subjective experience of acute pain: an assessment of the utility of 10 indices. Clin J Pain 1989;5:153–9.

Kosek E, Eckholm J, Hansson P. Sensory dysfunction in fibromyalgia patients with implications for pathogenic mechanisms. Pain 1996;68:375–83.

Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning (HNCS) fibromyalgia patients and healthy subjects. Pain 1997;70:41–51.

Lautenbacher S, Rollman GB, McCain GA. Multi-method assessment of experimental and clinical pain in patients with fibromyalgia. Pain 1994;59:45–53.

McDermid AJ, Rollman GB, McCain GA. Generalized hypervigilance in fibromyalgia: Evidence of perceptual amplification. Pain 1996;66:133–44.

Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30:191–7.

Petzke F, Khine A, Williams D, et al. Dolorimetry performed at 3 paired tender points highly predicts overall tenderness. J Rheumatol 2001;28:2568–9.

Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH. Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. Pain 2003;105:403–13.

Petzke F, Gracely RH, Park KM, Ambrose K, Clauw DJ. What do tender points measure? Influence of distress on 4 measures of tenderness. J Rheum 2003;30:567–74.

Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. Anesthesia 1976;31:1191–8.

Rollman GB, Lautenbacher S. Sex differences in musculoskeletal pain. Clin J Pain 2001;17:20–4.

Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. Pain 2001;91:165–75.

Staud R, Cannon RC, Mauderli AP, Robinson ME, Price DD, Vierck Jr CJ. Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. Pain 2003;102:87–95.

Weinberg SL, Goldberg KP. Basic statistics for education and the behavioral sciences. Boston, MA: Houghton Mifflin Company; 1979.

Wolfe FW, Smythe HA, Yunas MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum 1990;33:160–72.

The Journal of Pain, Vol 9, No 5 (May), 2008: pp 417-422
Available online at www.sciencedirect.com

A Psychophysical Study of Auditory and Pressure Sensitivity in Patients With Fibromyalgia and Healthy Controls

Michael E. Geisser,*,† Jennifer M. Glass,*,‡,§ Ljubinka D. Rajcevska,‖ Daniel J. Clauw,* David A. Williams,* Paul R. Kileny,¶ and Richard H. Gracely*

*Chronic Pain and Fatigue Research Center, Department of Internal Medicine, Division of Rheumatology, †Department of Physical Medicine and Rehabilitation, ‡Department of Psychiatry, §Institute for Social Research, University of Michigan, Ann Arbor, Michigan.
‖University Sv Kiril i Metodij, Skopje, Macedonia; and
¶Departments of Otolaryngology and Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, Michigan.

Abstract: Fibromyalgia (FM) is characterized by widespread tenderness. Studies have also reported that persons with FM are sensitive to other stimuli, such as auditory tones. We hypothesized that subjects with FM would display greater sensitivity to both pressure and auditory tones and report greater sensitivity to sounds encountered in daily activities. FM subjects (n = 30) and healthy control subjects (n = 28) were administered auditory tones and pressure using the same psychophysical methods to deliver the stimuli and a common way of scaling responses. Subjects were also administered a self-report questionnaire regarding sensitivity to everyday sounds. Participants with FM displayed significantly greater sensitivity to all levels of auditory stimulation (*P*s < .05). The magnitude of difference between FM patients' lowered auditory sensitivity (relative to control subjects) was similar to that seen with pressure, and pressure and auditory ratings were significantly correlated in both control subjects and subjects with FM. FM patients also were more sensitive to everyday sounds (t = 8.65, *P* < .001). These findings support that FM is associated with a global central nervous system augmentation in sensory processing. Further research is needed to examine the neural substrates associated with this abnormality and its role in the etiology and maintenance of FM.

***Perspective:** Muscle tenderness is the hallmark of FM, but the findings of this study and others suggest that persons with FM display sensitivity to a number of sensory stimuli. These findings suggest that FM is associated with a global central nervous system augmentation of sensory information. These findings may also help to explain why persons with FM display a number of comorbid physical symptoms other than pain.*

***Key words:** Fibromyalgia, audition, pain perception, chronic pain, pain sensitivity.*

Fibromyalgia (FM) is a disorder characterized by widespread pain and is frequently accompanied by comorbid somatic symptoms such as sleep disturbance, fatigue, and cognitive difficulties.[30] The diagnosis of FM is made based on the complaint of widespread pain and the presence of tenderness at a minimum of 11 of 18 specific "tender points" as defined by the American College of Rheumatology (ACR) criteria.[27] Although there is agreement that there is augmented pain processing in FM, the precise reason(s) for this are not yet clear.[15,29]

There is emerging evidence that instead of FM being primarily a disturbance in pain processing, there may be a more global disturbance in responsiveness to a variety of noxious and innocuous sensory stimuli. Previous research has shown that persons with FM display greater sensitivity to paired tactile and auditory stimuli,[21] innocuous heat,[11] and electrical stimulation compared with healthy control subjects.[17] In addition, several studies have reported that persons with FM exhibit greater sensitivity to auditory tones when compared with healthy

Received October 22, 2007; Revised December 10, 2007; Accepted December 18, 2007.
Supported in part by Department of the Army grant DAMD-17002-0018.
Address reprint requests to Dr. Michael E. Geisser, University of Michigan Health System, 325 E. Eisenhower Parkway, Ann Arbor, MI 48108. E-mail: mgeisser@umich.edu
1526-5900/$34.00

doi:10.1016/j.jpain.2007.12.006

control subjects and persons with rheumatoid arthritis.[6,19,20,22] Two studies reported that patients with FM do not display any physical abnormalities associated with ear disease,[4,28] but others report evidence of central nervous system (CNS) abnormalities while processing auditory stimuli, as reflected by evoked potentials[1,18,22,31] and brainstem responses.[26] Taken together, these studies suggest that persons with FM do not display peripheral acoustic abnormalities but differ from healthy control subjects in terms of central processing of sensory information.

Other research supports the hypothesis that FM may be characterized by a decrease in inhibition and/or an increase in facilitation of activity in neural systems controlling sensory responsiveness. Montoya et al[21] examined the ability of FM subjects and healthy control subjects to inhibit irrelevant somatosensory and auditory stimulation. The authors reported that FM subjects displayed abnormal information processing, characterized by lack of inhibitory control over repetitive nonpainful stimuli. Carrillo-de-la-Pena et al[6] examined evoked potentials in persons with FM and in healthy control subjects as a function of the intensity of the auditory stimulus. Persons with FM had shorter N1 and P2 latencies compared with healthy control subjects, and this relationship became more pronounced at higher stimulus intensities. The authors concluded that deficits in an inhibitory system may be responsible for some deficits observed in FM. More recently, Geisser et al (Geisser ME, Donnell CS, Petzke F, Gracely RH, Clauw DJ, Williams DA. Co-morbid somatic symptoms and functional status in patients with fibromyalgia and chronic fatigue syndrome: Sensory amplification as a common mechanism. Psychosomatics [unpublished report]) found that an index of sensory amplification (a composite measure of pressure sensitivity and ratings of perceived exertion during exercise at a specified workload) in FM subjects was associated with greater report of pain, physical symptoms, and lower physical function. These studies all support the notion that FM is characterized by heightened responsiveness to sensory stimulation.

Despite this emerging evidence that there may be a global problem with sensory processing in FM, few studies have presented FM patients with different stimuli using precisely the same testing paradigms to compare sensitivity across sensory systems. Moreover, most previous studies of sensory thresholds in FM have used "ascending" methods where the intensity of the stimulus is gradually increased. These methods led to reporting biases by subjects, and individuals who are more "expectant" or have higher levels of distress will rate a sensory experience as being more aversive or unpleasant than individuals who do not have these features.[23,24] Thus, it is possible that the previous findings of a decreased threshold to sensory stimuli could primarily be due to comorbid distress or expectancy among the FM participants (relative to the control subjects) rather than due to a fundamental defect in sensory processing.

In the present study, we examined both self-report and experimental sensitivity to the loudness of auditory tones in subjects with FM and normal, healthy control subjects. These same individuals were tested for their sensitivity to pressure, using the exact same paradigm in which the auditory tones were presented. This testing paradigm presents sensory stimuli in a random, unpredictable manner, and the results of this measure have previously been demonstrated to be unrelated to expectancy or distress on the part of subjects.[23,24] We hypothesized that subjects with FM would be more sensitive to both sound and pressure on psychophysical testing, consistent with prior studies, and that the ratings obtained for sound and pressure in FM subjects would be significantly related to each other. In addition, we also hypothesized that subjects with FM would perceive themselves as being more sensitive to sound.

Methods

Subjects

Participants were normal, healthy subjects and persons who met the 1990 American College of Rheumatology criteria for FM.[27] The research was approved by the University of Michigan Institutional Review Board, and informed consent was obtained from all participants before participation. Subjects were recruited from local advertisements and from persons who enrolled in a subject registry expressing interest to participate in research related to FM. Inclusion criteria for the study were 18 years of age or older and meeting the criteria for a healthy control or subject with FM. Exclusion criteria were significant hearing loss or disability (determined by self-report or hearing screening), the use of hearing aids, comorbid medical illness capable of causing a worsening of physical functional status independent of FM (eg, morbid obesity, autoimmune disease, cardiopulmonary disorders [eg, angina, congestive heart failure, chronic obstructive pulmonary disease, chronic asthma], uncontrolled endocrine or allergic disorders [eg, thyroid dysfunction, type I diabetes], and malignancy within 2 years), and having a psychiatric disorder involving a history of psychosis (eg, schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, etc), current suicide risk or attempt within 2 years of the study, or substance abuse within 2 years. Subjects with mood disorders were not excluded.

Thirty-one subjects with FM were recruited, in addition to 29 healthy control subjects. All subjects underwent pressure testing on 1 visit that was part of their participation in a research registry, for which separate informed consent was obtained. At the time of this visit, informed consent was obtained from subjects to complete the auditory screening, hyperacusis questionnaire, and undergo auditory stimulation at a subsequent visit. To be eligible for inclusion in this study, subjects had to return within 1 week to complete the auditory questionnaire and auditory testing. Two subjects (1 in each group) did not complete pressure testing within 1 week of the study visit. These 2 subjects were excluded, leaving 30 subjects with FM and 28 healthy control subjects.

The mean age of FM subjects was 42.1 years (SD = 9.0), and the mean age of control subjects was 37.8 years

(SD = 10.8). The groups did not significantly differ in age, based on an independent-samples *t* test. Twenty-eight of the 30 FM subjects were female and 24 of 28 control subjects were female.

Measures

Hearing Screening

A pass/fail hearing screening was performed on each participant according to the American Speech-Language-Hearing Association guidelines.[2] This involved a brief history questionnaire, otoscopic inspection, and a 25 dB HL pure-tone screen at 1000, 2000, and 4000 Hz and 35 dB HL at 500 Hz. Testing was conducted in a quiet environment, using disposable insert earphones. Persons who failed to respond to any of the tones were excluded from the remainder of the study.

Hyperacusis Questionnaire

All subjects completed the Hyperacusis Questionnaire.[3] This questionnaire assesses the real-life auditory experiences of respondents. Items measure what kinds of noises are bothersome and what levels of volume they find uncomfortable. The summary score was computed and analyzed for all subjects.

Pressure Stimulation

Pressure pain sensitivity was evaluated by subjective scaling of multiple pressure pain sensations. Discrete 5-second pressure stimuli were applied to the fixated left thumbnail with a 1-cm^2 hard rubber probe. Previous studies have shown that "neutral" regions, such as the thumb, accurately reflect an individual's overall pressure pain sensitivity.[25] The rubber probe was attached to a hydraulic piston, which was connected via a combination of valves to a second piston. Application of calibrated weights to the second piston produced controlled, repeatable pressure pain stimuli of rectangular waveform. Subjects rated the intensity of pressure pain sensations by using a combined numerical analog descriptor scale, developed from previously quantified verbal descriptors.[12] The Gracely box scale (GBS) lists the numbers 0 to 20 in descending order next to a set of verbal descriptors ranging from "extremely intense" (between 18 and 19) to "no pain sensation" (0). Subjects are asked to choose the number that best describes their pain. The session began with a series of stimuli presented in a predictable, "ascending" fashion, beginning at 0.5 kg/cm^2 and increasing in 0.5 kg/cm^2 intervals up to tolerance or to a maximum of 10 kg/cm^2. After the ascending series, 36 stimuli were delivered at 20-second intervals in random order, using the multiple random staircase (MRS) method.[14] The MRS method is response-dependent, that is, it determines the stimulus intensity needed to elicit a specified response. In this implementation, 3 independent staircases are titrated to produce pain sensations rated between 0 and 1 (no sensation to faint pain), between 9 and 10 (mild-moderate pain), and between 13 and 14 (strong-slightly intense pain) on the 0 to 20 GBS.

Auditory Stimulation

Judgments of Loudness Discomfort Levels (LDLs)[16] were obtained using methods similar to those using pressure stimulation described above. All tones were presented at 2000 Hz. Each ear was tested separately. First, a discrete ascending test was performed, and subjects rated the intensity of tones presented for 5 seconds at 40, 50, 60, 70, 80, 90, and 100 dB, using the GBS described above. Once this was completed, 36 stimuli were delivered at 20-second intervals in random order, using the MRS method described above. As for the pressure stimulation, 3 independent staircases were conducted to determine the intensity of the auditory tone needed to produce pain sensations rated between 0 and 1 (no sensation to faint pain), between 9 and 10 (mild-moderate pain), and between 13 and 14 (strong-slightly intense pain) on the 0 to 20 GBS. The process was then repeated for the other ear. The low-, medium-, and high-intensity levels from each ear were averaged for each subject.

Results

No subjects were excluded from the study, based on the findings of the hearing screening. Group differences on the various study measures are presented in Table 1. A low-intensity auditory level was not able to be obtained in at least 1 ear for 14 subjects in the study, as subjects did not provide a low enough rating on the GBS to the lowest stimulus intensity (40 dB). For these subjects, the lowest stimulus intensity (40 dB) was recorded as the low-stimulus intensity. Because of this "floor" effect on this particular measure, a nonparametric test (Mann–Whitney) test was used to compare FM subjects and healthy control subjects on this measure. Independent-group *t* tests were used for all other comparisons.

As expected, subjects with FM displayed greater sensitivity to pressure stimulation to the thumb compared with healthy control subjects for low-, medium-, and high-pressure intensities. The mean pressure needed to evoke these sensations for FM subjects were significantly lower than for healthy control subjects. As with pressure stimulation, significantly lower auditory stimulation was needed to evoke ratings of low, medium, and high pain intensity in FM subjects compared with healthy control subjects. In addition, subjects with FM reported having significantly greater hearing sensitivity on the hyperacusis questionnaire compared with healthy control subjects.

Pearson correlation coefficients were computed to examine the relationship between auditory ratings and pressure ratings first in healthy control subjects and then in FM subjects. Given that some subjects were assigned a "floor" value for the low intensity auditory condition, Spearman rank-order correlations were computed for this variable instead of Pearson correlations.

The data for healthy control subjects are presented in Table 2. The low auditory and pressure stimuli were significantly correlated with each other, as well as the medium auditory and pressure intensities. The correlation between the high auditory and pressure stimuli was of

Table 1. Group Means and Standard Deviations for Self-Report of Hearing Sensitivity and Ratings of Low, Medium, and High Auditory and Pressure Stimulation in Subjects With FM and Healthy Control Subjects

		Group	
Variable	FM Mean (SD)	Healthy Control Subjects Mean (SD)	t value or Z
Hyperacusis Questionnaire score	13.8 (5.2)	4.1 (3.0)	8.65‡
Pressure-low intensity (kg/cm^2)	0.48 (0.48)	1.1 (0.91)	3.23†
Pressure-medium intensity (kg/cm^2)	1.62 (0.94)	2.92 (1.74)	3.53†
Pressure-high intensity (kg/cm^2)	3.07 (1.37)	4.35 (1.87)	2.96†
Auditory-low intensity§ (dB)	48.0 (10.8)	56.4 (14.5)	2.04*
Auditory-medium intensity (dB)	69.0 (12.3)	78.5 (12.6)	2.90†
Auditory-high intensity (dB)	81.3 (9.8)	88.5 (7.9)	3.07†

*$P < .05$.

†$P < .01$.

‡$P < .001$.

§Mann–Whitney test was conducted instead of *t* test.

moderate size[7] but failed to achieve statistical significance ($r = .32$, $P = .095$).

The correlations between auditory and pressure stimulation in FM subjects are presented in Table 3. Medium auditory and pressure stimulation were significantly associated with each other, but the association between the extreme low- and high-intensity pairs were of moderate size but not statistically significant ($r = .29$, $P = .114$ and $r = .35$, $P = .057$, respectively). Low-intensity pressure stimuli were significantly associated with the medium- and high-intensity auditory stimuli, and medium pressure stimulation was significantly associated with high-intensity levels of auditory stimulation.

Discussion

Consistent with prior research, subjects with FM demonstrated greater sensitivity to auditory tones compared with healthy control subjects. They also reported significantly greater sensitivity to daily sounds. Within both the patient and control groups, sound and pressure sensitivity measures were related to each other, suggesting a common underlying mechanism associated with these phenomena. Thus, these data lend further credence to the notion that FM is in part due to a global disturbance in sensory processing rather than an isolated abnormality in pain processing.

Strengths of the present study include the use of standardized methods to assess responses to pressure and auditory stimulation, making the responses to these different types of stimuli directly comparable. Significant associations were observed between auditory and pressure responses in subjects with FM as well as healthy control subjects. The fact that responses to auditory and pressure stimulation in subjects with FM were significantly associated with each other supports the notion that these abnormalities may be related to a common underlying pathophysiological mechanism. It would be beneficial to examine whether interventions for FM that alter treatment tenderness also affect the processing of other stimuli such as auditory tones.

One limitation of the present study is the cross-sectional design. Given this, one cannot determine whether the abnormalities observed in FM subjects are a cause or a consequence of FM. In addition, the sample sizes exam-

Table 2. Correlations Between Pressure and Auditory Measures in Healthy Control Subjects

Variable	2	3	4	5	6
1. Pressure: low intensity	.79‡	.60†	.52†	.26	.28
2. Pressure: medium intensity		.92‡	.39*	.37*	.35
3. Pressure: high intensity			.30	.31	.32
4. Auditory: low intensity§				.63‡	.55†
5. Auditory: medium intensity					.92‡
6. Auditory: high intensity					

*$P < .05$.

†$P < .01$.

‡$P < .001$.

§Correlations with auditory-low intensity are Spearman rank-order correlations. All others are Pearson correlations.

Table 3. Correlations Between Pressure and Auditory Measures in FM Subjects

Variable	2	3	4	5	6
1. Pressure-low intensity	.53†	.30	.29	53†	.43*
2. Pressure-medium intensity		.81‡	.14	.40*	.36*
3. Pressure-high intensity			.09	.28	.35
4. Auditory-low intensity§				.63‡	.47†
5. Auditory-medium intensity					.81‡
6. Auditory-high intensity					

*$P < .05$.

†$P < .01$.

‡$P < .001$.

§Correlations with auditory-low intensity are Spearman rank-order correlations. All others are Pearson correlations.

ined were small, and some of the statistical tests lacked power such that moderate effect sizes that were observed were not statistically significant. Last, the auditory methods used were somewhat novel, and a floor effect was observed for auditory stimulation in some subjects as they gave consistently high ratings to the lowest stimulus intensity (40 dB). Future studies using these methods may wish to include lower auditory stimulus intensities.

It should be noted that the differences in auditory sensitivity between FM and healthy control subjects observed in the present study are lower than the difference reported previously by McDermid et al.[20] In the present study, FM subjects perceived auditory stimuli to be of the same intensity compared with control subjects when the intensity of the stimulus was approximately 8 dB lower in intensity. McDermid et al observed a mean difference in auditory pain thresholds between FM patients and control subjects that was approximately 30 dB. It is possible that this in part may be due to sample differences. Another possible reason for the smaller group differences observed in the present study was the use of the random staircase method to examine sensation. Prior research conducted by Petzke et al[25] demonstrated that gradually ascending measures of stimulation, as used in McDermid et al study, are significantly and negatively associated with measures of mood or negative affect. Petzke et al suggest that persons who are distressed or anxious persons may terminate a stimulus prematurely in anticipation of pain when experiencing gradually increasing stimulation. Random methods of stimulation were not significantly associated with measures of mood in this study, suggesting that these measures are less prone to biases associated with negative affect. Thus, the larger effect size observed in the McDermid et al[20] study may be due to the additional influence of negative affect on pain threshold determinations among subjects with FM, as pain populations have consistently been shown to experience greater psychological distress compared with healthy populations.

Neuroimaging studies have reported that subjects with FM have heightened brain responses to evoked pain sensations,[5,8,13,15] including structures such as the insula. Regions of the insula are proposed to be involved in an interoceptive system that is activated in response to sensations arising from within the body including pain, temperature, itch, sensual touch, hunger, thirst, and muscular and visceral sensations.[9,10] It is possible that dysfunction of this interoceptive system may be involved in the sensitivity to various stimuli observed in persons with FM. In future studies, neuroimaging techniques should be used to examine whether subjects with FM display heightened responses in the insula compared with healthy control subjects in response to nonpainful stimuli such as auditory tones.

The present study supports the notion that FM is associated with a central nervous system deficit in sensory processing. Future research is needed to examine the pathophysiological mechanisms associated with these perceptual abnormalities, and the role that these abnormalities play in the etiology and maintenance of FM. In addition, it would be beneficial to examine whether these abnormalities are unique to FM or whether they are associated with other chronic pain conditions as well.

References

1. Alanoglu E, Ulas UH, Ozdag F, Odabasi Z, Cakci A, Vural O: Auditory event-related brain potentials in fibromyalgia syndrome. Rheumatol Int 25:345-349, 2005

2. American Speech-Language-Hearing Association. Guidelines for audiologic screening. Rockville, MD, American Speech-Language-Hearing Association, 1997

3. Andersson G, Lindvall N, Hursti T, Carlbring P: Hypersensitivity to sound (hyperacusis): A prevalence study conducted via the Internet and post. Int J Audiol 41:545-554, 2002

4. Bayazit YA, Gursoy S, Ozer E, Karakurum G, Madenci E: Neurotologic manifestations of the fibromyalgia syndrome. J Neurol Sci 196:77-80, 2002

5. Bradley LA, McKendree-Smith NL, Alberts KR, Alarcon GS, Mountz JM, Deutsch G: Use of neuroimaging to understand abnormal pain sensitivity in fibromyalgia. Curr Rheumatol Rep 2:141-148, 2000

6. Carrillo-de-la-Pena MT, Vallet M, Perez MI, Gomez-Perretta C: Intensity dependence of auditory-evoked cortical potentials in fibromyalgia patients: A test of the generalized hypervigilance hypothesis. J Pain 7:480-487, 2006

7. Cohen J: Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillsdale, NJ, Lawrence Erlbaum Associates, 1988

8. Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH: Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol 31:364-378, 2004

9. Craig AD: Interoception: The sense of the physiological condition of the body. Curr Opin Neurobiol 13:500-505, 2003

10. Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ: Neural systems supporting interoceptive awareness. Nat Neurosci 7:189-195, 2004

11. Geisser ME, Casey KL, Brucksch CB, Ribbens CM, Appleton BB, Crofford LJ: Perception of noxious and innocuous heat stimulation among healthy women and women with fibromyalgia: Association with mood, somatic focus, and catastrophizing. Pain 102:243-250, 2003

12. Gracely RH, Dubner R, McGrath PA: Narcotic analgesia: Fentanyl reduces the intensity but not the unpleasantness of painful tooth pulp sensations. Science 203:1261-1263, 1979

13. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ: Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain 127:835-843, 2004

14. Gracely RH, Lota L, Walter DJ, Dubner R: A multiple random staircase method of psychophysical pain assessment. Pain 32:55-63, 1988

15. Gracely RH, Petzke F, Wolf JM, Clauw DJ: Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 46:1333-1343, 2002

16. Keidser G, Seymour J, Dillon H, Grant F, Byrne D: An efficient, adaptive method of measuring loudness growth functions. Scand Audiol 28:3-14, 1999

17. Lautenbacher S, Rollman GB, McCain GA: Multi-method assessment of experimental and clinical pain in patients with fibromyalgia. Pain 59:45-53, 1994

18. Lorenz J. Hyperalgesia or hypervigilance? An evoked potential approach to the study of fibromyalgia syndrome. Zeitschrift fur Rheumatologie 57(Suppl 2):19-22, 1998

19. Lorenz J, Grasedyck K, Bromm B: Middle and long latency somatosensory evoked potentials after painful laser stimulation in patients with fibromyalgia syndrome. Electroencephalogr Clin Neurophysiol 100:165-168, 1996

20. McDermid AJ, Rollman GB, McCain GA: Generalized hypervigilance in fibromyalgia: Evidence of perceptual amplification. Pain 66:133-144, 1996

21. Montoya P, Sitges C, Garcia-Herrera M, Rodriguez-Cotes A, Izquierdo R, Truyols M, Collado D: Reduced brain habituation to somatosensory stimulation in patients with fibromyalgia. Arthritis Rheum 54:1995-2003, 2006

22. Ozgocmen S, Yoldas T, Kamanli A, Yildizhan H, Yigiter R, Ardicoglu O: Auditory P300 event related potentials and serotonin reuptake inhibitor treatment in patients with fibromyalgia. Ann Rheum Dis 62:551-555, 2003

23. Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH: Increased pain sensitivity in fibromyalgia: Effects of stimulus type and mode of presentation. Pain 105:403-413, 2003

24. Petzke F, Gracely RH, Khine A, Clauw DJ: Pain sensitivity in patients with fibromyalgia (FM): Expectancy effects on pain measurements. Arthritis Rheum 42(9, Suppl):S342, 1999

25. Petzke F, Gracely RH, Park KM, Ambrose K, Clauw DJ: What do tender points measure? Influence of distress on 4 measures of tenderness. J Rheumatol 30:567-574, 2003

26. Rosenhall U, Johansson G, Orndahl G: Neuroaudiological findings in chronic primary fibromyalgia with dysesthesia. Scand J Rehabil Med 19:147-152, 1987

27. Wolfe FW, Smythe HA, Yunas MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA, Reynolds WJ, Romano TJ, Russell IJ, Sheon RP: The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia: Report of the Multicenter Criteria Committee. Arthritis Rheum 33:160-172, 1990

28. Yilmaz M, Baysal E, Gunduz B, Aksu A, Ensari N, Meray J, Bayazit YA: Assessment of the ear and otoacoustic emission findings in fibromyalgia syndrome. Clin Exp Rheumatol 23: 701-703, 2005

29. Yunus MB: Towards a model of pathophysiology of fibromyalgia: Aberrant central pain mechanisms with peripheral modulation. J Rheumatol 19:846-850, 1992

30. Yunus MB: Symptoms and signs of fibromyalgia syndrome: An overview, in Wallace DJ, Clauw DJ (eds): Fibromyalgia and Other Central Pain Syndromes. Philadelphia, PA, Lippincott Williams & Wilkins, 2005, pp 125-132

31. Yoldas T, Ozgocmen S, Yildizhan H, Yigiter R, Ulvi H, Ardicoglu O: Auditory p300 event-related potentials in fibromyalgia patients. Yonsei Med J 44:89-93, 2003

Comorbid Somatic Symptoms and Functional Status in Patients With Fibromyalgia and Chronic Fatigue Syndrome: Sensory Amplification as a Common Mechanism

MICHAEL E. GEISSER, PH.D., CATHY STRADER DONNELL, PH.D.
FRANK PETZKE, M.D., RICHARD H. GRACELY, PH.D.
DANIEL J. CLAUW, M.D., DAVID A. WILLIAMS, PH.D.

Background: *Somatic symptoms are common in conditions such as fibromyalgia (FM) and chronic fatigue syndrome (CFS).* **Objective:** *Authors investigated a potential shared pathologic mechanism: a generalized perceptual abnormality where there is heightened responsiveness to varied sensory stimulation, including pain.* **Method:** *A composite measure of sensory sensitivity was created and compared with measures of somatic symptoms, comorbid psychological disturbances, and self-reported physical functioning in 38 patients with FM and/or CFS.* **Results:** *Sensory amplification influenced physical functioning indirectly through pain intensity, and physical symptoms and fatigue also independently contributed to physical functioning.* **Conclusion:** *Sensory amplification may be an underlying pathophysiologic mechanism in these disorders that is relatively independent of depression and depressive symptoms.*

(Psychosomatics 2008; 49:235–242)

The diagnoses of fibromyalgia (FM) and chronic fatigue syndrome (CFS) emphasize pain and fatigue, respectively, as the hallmark symptoms of each condition.[1,2] These conditions and other chronic multi-symptom illnesses are not discrete, but rather share symptoms such as pain, fatigue, sleep disturbance, and memory problems.[1,3] Although some literature suggests that the presence of numerous comorbid physical symptoms among persons with FM and CFS is suggestive of somatization disorder,[4] others propose that the presence of comorbid physical symptoms suggests shared underlying pathogenic mechanisms.[5,6]

One potential shared pathologic mechanism is a generalized perceptual abnormality whereby persons display heightened responsiveness to varied sensory stimulation, including painful stimulation. Whereas increased pressure-pain sensation is the hallmark of FM, research has shown that persons with FM also display greater sensitivity to other stimuli, such as auditory tones,[7–10] paired tactile and auditory stimuli,[11] innocuous heat,[12] and electrical stimulation.[13] These studies suggest that FM could be characterized by a decrease in inhibition and/or an increase in facilitation of activity in neural systems controlling sensory responsiveness. This spectrum of illness might be best characterized as a condition of generalized sensory amplification of bodily experiences that includes, but is not limited to, complaints of pain.

Depression is a candidate factor that may be responsible for sensory amplification in FM. Multiple comorbid physical symptoms are common among persons with major depression, and it has been suggested that the heightened

Received February 20, 2007; accepted June 18, 2007. From the Chronic Pain and Fatigue Research Center, Dept. of Internal Medicine, Div. of Rheumatology, Univ. of Michigan, Ann Arbor, MI; the Dept. of Physical Medicine and Rehabilitation, Univ. of Michigan, Ann Arbor, MI; and the Univ. of Cologne, Cologne, Germany. Send correspondence and reprint requests to Michael E. Geisser, Ph.D., Univ. of Michigan Health System Dept. of Anesthesiology and Intensive Care, 325 E. Eisenhower Parkway, Ann Arbor, MI 48108. e-mail: mgeisser@med.umich.edu

awareness of bodily sensations that accompanies depression explains some of the perceptual abnormalities associated with chronic pain.[14] However, studies in patients with FM suggest that depression and somatization function independently of sensory augmentation.[11] This independence of pain processing and depressive symptoms or depression has also been noted in a functional-MRI study in FM showing that the presence of depressive comorbidity did not influence the degree of pain-evoked neuronal activation in regions of the brain that code for the sensory dimension of pain.[15] Sayar et al.[16] reported that depression and sensory amplification both decreased in subjects with major depression after treatment. However, in patients with FM, only depression, but not sensory amplification, decreased after treatment. The authors concluded that sensory amplification has a more enduring association with FM, such that relief from depression does not alter this relationship.

Wolfe and colleagues[17] suggested that all patients with rheumatic diseases have variable levels of sensory amplification. These authors examined comorbid conditions in 1,298 patients with FM, as compared with 2,396 patients with rheumatoid arthritis or osteoarthritis. FM patients reported significantly more comorbid medical conditions (e.g., depression, infections, diverticulitis, and allergies) than did patients with rheumatoid arthritis or osteoarthritis. Also, FM subjects rated these comorbid symptoms as being important or having a serious impact on their health. Although FM subjects reported the greatest number of comorbid conditions, individuals in all groups reported a high number of comorbid conditions, and this measure was continuously distributed over the entire large combined cohort. Given the large number of comorbid conditions observed in FM and CFS, it is likely that symptoms other than pain and fatigue contribute to the very low levels of physical functioning observed in these populations.[18–20]

The present study is the first that we are aware of to develop an experimental measure of sensory sensitivity and then compare this measure to clinical assessment of somatic symptoms, self-reported functional status, and depressive symptoms. To explore these relationships simultaneously, we constructed a path-analytic model utilizing multiple-regression analysis to calculate the path coefficients.

METHOD

Subjects

Participants were 38 subjects who either met the 1990 American College of Rheumatology criteria for FM[2] or who fulfilled the diagnostic criteria for CFS.[1] The research was approved by the Georgetown University Medical Center and University of Michigan institutional review boards, and informed consent was obtained from all participants before their participation. All patients underwent a comprehensive screening exam during which the diagnosis was confirmed and the presence of comorbid symptoms was evaluated. Exclusion criteria were severe physical impairment, medical conditions that were capable of causing patients' symptoms (e.g., morbid obesity, autoimmune/inflammatory diseases, cardiopulmonary disorders), uncontrolled endocrine or allergic disorders (i.e., hyper-/hypothyroidism, diabetes, allergic rhinitis), malignancy, severe psychiatric illnesses (e.g., schizophrenia, addiction disorders), factors known to affect the hypothalamic–pituitary axis or autonomic functioning (e.g., cigarette smoking, daily intake of caffeine exceeding the equivalent of 2 cups of coffee), or medication usage other than as-needed analgesics (excluding long-term narcotics).

Self-Report Measures

Pain Pain ratings were measured with the short form of the McGill Pain Questionnaire (MPQ–SF),[21] which measures the quality of pain by asking patients to rate their pain relative to the quality implied by 15 verbal descriptors of pain on a 0-to-3 rating scale. The Pain Rating Index (PRI) comprises two scores: 1) a sensory pain score; and 2) an affective pain score. In this study, the PRI is used as the measure of pain intensity.

Depression The Center for Epidemiological Studies–Depression Scale (CES–D)[22] was used to assess self-report of depressive symptoms. The measure is a 20-item questionnaire in which patients rate the frequency of depressive symptoms on a 0-to-3 scale relative to how they felt during the past week. A total score is obtained by summing all responses, with higher scores reflecting greater depressive symptoms. The scale is reported to be valid among persons with physical disabilities[23] and has good sensitivity and specificity in chronic-pain populations.[24,25]

Fatigue Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI).[26] The MFI consists of 20 items that can be scored to yield five scale dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation, and Reduced Activity. This inventory has been validated in samples of cancer patients, medical students,

army recruits, and junior physicians. For the purpose of this study, the General Fatigue scale was used.

Physical Symptoms The number of comorbid physical symptoms was obtained from a standardized symptom checklist (SxList). This self-report checklist instructs participants to indicate whether or not they experienced each of 51 symptoms for at least 3 months over the past year. A total score was obtained by summing Yes responses to all 51 symptoms. Sample symptoms include dry eyes, shortness of breath, dizziness, irregular heartbeat, tingling in the extremities, urinary urgency, and coughing spells. Three items, assessing muscle pain, persistent fatigue, and extreme fatigue, were excluded from the total score because these items overlapped with the hallmark symptoms and could not be considered to be comorbid. Reliability (internal consistency) of this scale with the three items eliminated in the present sample was found to be 0.91.

Physical Functional Status The Medical Outcomes Survey Short Form–36 (SF–36) is a self-administered patient-reported outcome (PRO) measure of health-related quality of life.[27,28] The eight domains of health-related quality of life assessed by the SF–36 are the following: 1) physical functioning; 2) role limitations because of physical problems; 3) bodily pain; 4) general health perceptions; 5) energy/vitality; 6) social functioning; 7) role limitations due to emotional problems; and 8) mental health. Also, two summary scores: Physical Component (PCS) and Mental Component (MCS) are derived by combining and positively or negatively weighting all eight domains. Scores for all domain and summary measures are transformed to z-scores ranging between 0 and 100, with lower scores indicative of poorer functioning. In this study, only the PCS score was examined.

Measures of Sensory Amplification

Pressure Stimulation Previous studies have shown that "neutral" regions, such as the thumb, in individuals with FM, accurately reflect an individual's overall pressure-pain sensitivity.[29] Pressure-pain sensitivity was evaluated by subjective scaling of sensations evoked by discrete 5-second pressure stimuli applied to the fixed thumbnail with a 1-cm^2 hard rubber probe, using the Multiple Random Staircase (MRS) method.[30] The delivery of the MRS is driven by an interactive software system that presents stimuli in a random manner, facilitating the identification of stimulus-intensity values associated with subjective ratings between 0 and 1 (no sensation-to-faint pain), between 9 and 10 (mild-to-moderate pain), and between 13 and 14 (strong-to-slightly intense pain) on the 0–20 box scale.(31) For this study, stimulus values eliciting mild-to-moderate pain were used.

Ratings of Perceived Exertion Subjects underwent a submaximal exercise test on an electronically-braked cycle ergometer (Sensormedics; Yorba Linda, CA). The test was graded, with 3-minute stages culminating when the subjects' heart rate reached 85% of their age-predicted maximum. After 1 minute of unloaded pedaling, Stage 1 was set at either 25 or 50 watts (W). For Stage 2, depending upon the subject's response during the first stage, the workload was increased by either 25 or 50 W. Both objective and subjective responses were taken into consideration. Subsequent increases in workload came in 25-W increments every 3 minutes. Ratings of perceived exertion were recorded once per stage with the Borg 6–20 scale.[32] Borg scores range from 6 (very, very light) to 20 (very, very heavy). An amplification measure for exercise was obtained by dividing the rating of perceived exertion by the workload (watts) during the first stage of exercise. Using this measure, a previous study found that subjects with FM reported consistently greater perceived exertion per workload during exercise than did healthy-control subjects.[33]

Index of Sensory Amplification We constructed an index of sensory amplification (ISA) by determining the z-score from the sample mean and standard deviation (SD) for each person for the pressure-intensity (kg) needed to evoke mild-to-moderate pain, and the z-score for the amplification measure for exercise (perceived exertion/W). Higher ratings on the exercise amplification measure represented greater augmentation, and augmentation of pressure sensitivity corresponded with lower scores on this measure. To facilitate the creation of a composite index, scores on the pressure-sensitivity measure were multiplied by -1, making the scaling and directionality of both measures equivalent. Finally, the z-scores were averaged to calculate a composite index. Thus, higher (more positive) scores on this measure are associated with greater sensory amplification.

Statistical Analyses

Statistical analyses required three steps. First, zero-order (Pearson) correlations were calculated in order to determine the strength of association between the ISA and

the hallmark symptoms of FM and CFS (i.e., pain and fatigue), comorbid physical concerns, and depression. Similarly, correlations were also calculated with the PCS score from the SF–36 to assess the relative strength of association between each of the previously-mentioned variables and physical functional status.

Second, correlations between the pressure-sensitivity measure, perceived exertion measure, and ISA were examined to determine whether the patterns of correlations between the individual and composite measures were similar. This was done to examine whether the individual measures of sensory augmentation were both related to the variables of interest, rather than one individual scale being responsible for any observed associations with the composite measure.

The third step involved the construction of a path-analytic model utilizing multiple-regression techniques to examine the proposed interrelationships between the defined variables when the other variables were considered simultaneously.[34] Standardized regression coefficients were calculated to determine the path coefficients, with physical-functional status serving as the dependent outcome measure. Contrary to our hypothesis, if the zero-order correlations revealed a significant association between depression and the ISA, depression would be entered into the model first, followed by ISA. If not, assuming the ISA to be a common mechanism in the erosion of physical functioning, ISA was entered first into the model, followed by hallmark symptoms and the number of comorbidities serving as mediating variables. The path coefficient between the ISA and each of the mediators was calculated as the partial regression coefficient between ISA and each of the symptom-measures controlling for the other symptom-measures. The path coefficient between each of the mediators and physical functioning was calculated by determining the standardized regression coefficient between the mediator and PCS, simultaneously controlling for the other mediators and sensory amplification.

Finally, the direct relationship between the ISA and physical functioning was calculated by determining the standardized regression coefficient between these two variables, controlling for all of the mediators. Given the colinearity between some of the variables and the conservative nature of this analysis, the criterion for statistical significance was set at $p<0.10$.

RESULTS

Table 1 lists the demographic and descriptive statistics for each of the measures used in this study. Eight subjects fulfilled only the diagnostic criteria for FM; 7, only the criteria for CFS; and 23 met criteria for both; 28 subjects were women, and 10 were men. The average age of participants was 42.0 years (standard deviation [SD]: 8.8), and the mean duration of pain was 87.9 months (SD: 64.4). The demographic characteristics of the sample are similar to those of previously published samples in both the FM and CFS literature,[17,35] although subjects in the present study were younger. Like other samples, over 90% complained of both pain and fatigue, and the mean number of items endorsed on the symptom checklist (SxList) was 19.2 (SD: 9.7).

Two subjects in the sample did not complete the submaximal stress test, and therefore an ISA could not be determined for them. In these two cases, imputation was facilitated by using the sample mean for the ISA and perceived exertion per watt.

The correlations between the individual and composite measures of sensory amplification are presented in Table 2. The individual amplification scales (i.e., pressure and exertion) were significantly correlated with each other ($r=0.43$; $p<0.01$), and both pressure sensitivity and perceived exertion were highly correlated with the composite score ($r=0.85$; $p<0.01$ and $r=0.84$; $p<0.01$, respectively). Both individual measures were significantly correlated with pain. Each showed an opposite, but nonsignificant relationship to fatigue. Both measures were inversely correlated with functioning, but only the relationship with perceived exertion was statistically significant. Neither measure was significantly related to depression. Both indexes were positively correlated with comorbid symptoms (the correlation with perceived exertion approached significance, at $p=0.07$). The pattern of correlations suggests that the individual measures of sensory amplification each contribute to relationships observed with the composite index.

The zero-order correlations are presented in Table 3. Greater sensory sensitivity to evoked stimuli, as defined by the ISA, was significantly associated with greater pain intensity, poorer physical functioning, and a greater number of comorbid physical symptoms. Depressive symptoms were not significantly associated with the ISA or the other variables of interest, except that greater depressive symptoms were significantly associated with greater fatigue. The ISA did not show a significant relationship with fatigue. Pain was significantly associated with the number of comorbid secondary symptoms, but fatigue showed weak relationships with both pain and number of comorbidities. Self-reported physical functional status was significantly

associated with pain, fatigue, and the number of comorbid somatic symptoms.

The path model is presented in Figure 1. Because depression was not significantly associated with the ISA, this variable was eliminated from the model. Together, the remaining four predictor variables accounted for 50% of the variance in physical functioning, and the multiple-regression coefficient was statistically significant ($F = 8.37$; $p < 0.001$). The path coefficient between the ISA and physical functioning, controlling for the mediators (specific symptoms) in the model, was not statistically significant, suggesting that this variable only weakly contributes directly to physical functional status. However, the indirect pathway, through pain intensity as a mediating variable, was significant; the ISA was significantly associated with pain intensity, which, in turn, was significantly associated with physical functional status (controlling for sensory amplification and the other mediating variables in this latter pathway). The indirect pathway through physical symptoms was significant as well, using the same method of calculation. Greater fatigue was significantly associated with poorer physical functioning, but the pathway between the ISA and fatigue was not statistically significant, suggesting that the influence of fatigue on physical functional status may be due to a different mechanism.

DISCUSSION

Sensory amplification, as measured by a composite measure of pressure and perceived exertion during exercise, was significantly associated with higher clinical pain and a greater number of comorbid somatic symptoms. As hypothesized, this measure was not significantly associated with depressive symptoms. Contrary to our hypothesis, sensory amplification did not appear to have a strong association with fatigue, which suggests that fatigue may operate via a different underlying mechanism. Also, the path-analytic model suggested that sensory amplification only weakly independently affected physical functioning (when controlling for physical symptoms), but influenced outcomes through the origination or maintenance of multiple physical symptoms. These findings support the hypothesis that physical symptoms other than the hallmark symptoms of pain and fatigue significantly contribute to the poor physical functioning in FM and CFS. It is likely that a tendency toward sensory amplification would contribute to symptoms across many systems of the body where sensory perception is involved. It also makes sense that fatigue, which is not directly tied to specific sensory mechanisms, would show a poorer relationship with this index.

The findings also lend further support to the notion

TABLE 1. Sample Characteristics, Mean (Standard Deviation)

Variable	
Age, years	42.0 (8.8)
Pain duration, months	87.9 (64.4)
Gender	28 (73.6%) women, 10 (26.4%) men
Race	24 (63.2%) Caucasian, 5 (13.2%) African American, 4 (10.5%) Hispanic, 2 (5.3%) Asian or Pacific Islander, 3 (7.9%) other
McGill Pain Questionnaire (MPQ) Total	11.3 (8.1)
Multidimensional Fatigue Inventory (MFI): General Fatigue	16.6 (2.7)
Number of physical symptoms	19.2 (9.7)
Multiple Random Staircase (MRS) medium pressure sensitivity (kg/cm^2)	3.01 (2.1)
Perceived exertion per watt	0.32 (0.11)

TABLE 2. Correlations Among the Individual and Composite Measures of Sensory Augmentation and Depression, Hallmark Symptoms, Comorbid Fatigue, and Physical Functioning

Variable	Pressure Sensitivity	Perceived Exertion per Watt	ISA
Pain	0.34*	0.45**	0.45**
Fatigue	0.15	−0.16	−0.01
Physical Functioning	−0.36*	−0.20	−0.32*
Depression	0.13	0.14	0.16
Comorbidities	0.29	0.38*	0.41*

ISA: index of sensory amplification.
*$p < 0.05$; **$p < 0.01$.

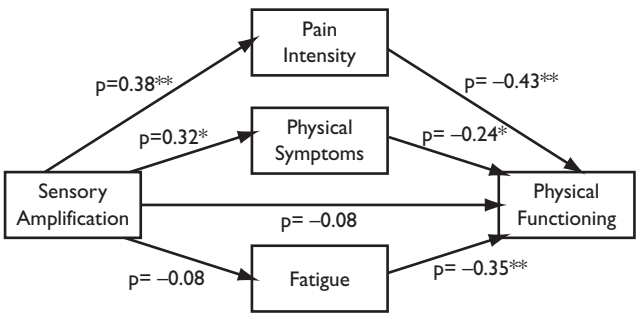
TABLE 3. Correlations Between Sensory Augmentation, Depression, Hallmark Symptoms, Comorbid Physical Symptoms, and Physical Functioning

Variable	Pain	Fatigue	Comorbidities	Physical Functioning	Depressive Symptoms
ISA	0.45**	−0.01	0.41*	−0.32*	0.16
Pain		0.12	0.34*	−0.57**	0.22
Fatigue			0.02	−0.41*	0.34*
Comorbidities				−0.41*	0.08
Physical Functioning					0.07

ISA: index of sensory amplification.
*p<0.05; **p<0.01.

that sensory amplification in subjects with FM is not due to somatization associated with depression. Several other studies have reported similar findings.[7,11,16,36] Instead, these data support the hypothesis that FM is characterized by altered central sensory processing mechanisms that are not limited to pain. Recent neuroimaging studies suggest that subjects with FM have heightened brain responses to evoked pain sensations.[37,38] The insula is consistently activated in these pain studies. Various regions of the insula are believed to be involved in an interoceptive system that is activated in response to sensations arising from within the body; these include pain, temperature, itch, sensual touch, hunger, thirst, and muscular and visceral sensations.[39,40] It is possible that dysfunction of this interceptive system, involving the insula, may be involved in the sensory amplification observed in FM. It would be interesting to determine whether subjects with FM display heightened responses in the insula in response to non-painful stimuli (such as auditory tones) as compared with healthy-control subjects.

FIGURE 1. Path Model Examining the Direct and Indirect Influence of Sensory Amplification on Physical Functioning With Pain Intensity, Physical Symptoms, Fatigue, and Attention/Concentration Symptoms as Mediating Variables



*p<0.10; **p<0.05.

The lack of association between sensory amplification and fatigue, the hallmark symptom of CFS, raises several possibilities. Although many of the comorbidities are shared between FM and CFS, making them appear to be similar, it is possible that the hallmark symptoms emanate from distinctly different mechanisms.[41] It is also possible that the lack of relationship between sensory amplification and fatigue is in part due to the chronicity of symptoms in this sample. Subjects had an average symptom duration of approximately 7 years. Although fatigue may initially be associated with sensory amplification, much like the other comorbid symptoms, over time, fatigue may become more influenced by other factors, such as inactivity and deconditioning. Future research may need to assess the relationship between sensory amplification and fatigue with newly-diagnosed conditions in order to gain insight into this relationship.

Supporting the confidence one can have in theses findings is the observation that statistically significant and meaningful relationships emerged from these data with a relatively small sample size. A potential limitation of the sample size is that other, weaker relationships requiring greater power to detect were missed. A second potential limitation was that the path-analytic model was fairly conservative, since the effects of any particular variable were examined while controlling for the influence of all other variables in the model. Although a conservative approach is appropriate for exploratory purposes, future studies, building upon these results, may be enlightened by replicating these findings using less conservative methods.

In summary, the findings of this study support the hypothesis that many symptoms in FM and CFS are associated with perceptual abnormalities (i.e., sensory amplification), and this deficit may be a common mechanism underlying these disorders. Future studies will need to replicate these findings in a larger sample and examine other sensory modalities such as auditory, olfactory, and visual

stimuli. Treatment implications of these findings suggest that management strategies may want to focus on dampening sensory amplification, in general; rather than treating each symptom in isolation.

References

1. Fukuda K, Straus SE, Hickie I, et al, and the International Chronic Fatigue Syndrome Study Group: The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994; 121:953–959
2. Wolfe FW, Smythe HA, Yunus MB, et al: The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Arthritis Rheum 1990; 33:160–172
3. Yunus MB: Symptoms and signs of fibromyalgia syndrome: an overview, in Fibromyalgia and Other Central Pain Syndromes. Edited by Wallace DJ, Clauw DJ. Philadelphia, PA, Lippincott, Williams & Wilkins, 2005, pp 125–132
4. Katon W, Sullivan M, Walker E: Medical symptoms without identified pathology: relationship to psychiatric disorders, childhood and adult trauma, and personality traits. Ann Intern Med 2001; 134:917–925
5. Clauw DJ: The pathogenesis of chronic pain and fatigue syndromes, with special reference to fibromyalgia. Med Hypotheses 1995; 44:369–378
6. Clauw DJ, Chrousos GP: Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 1997; 4:134–153
7. Carrillo-de-la-Peñna MT, Vallet M, Pérez MI, et al: Intensity dependence of auditory-evoked cortical potentials in fibromyalgia patients: a test of the generalized hypervigilance hypothesis. J Pain 2006; 7:480–487
8. Lorenz J, Grasedyck K, Bromm B: Middle- and long-latency somatosensory evoked potentials after painful laser stimulation in patients with fibromyalgia syndrome. EEG Clin Neurophysiol 1996; 100:165–168
9. McDermid AJ, Rollman GB, McCain GA: Generalized hypervigilance in fibromyalgia: evidence of perceptual amplification. Pain 1996; 66:133–144
10. Ozgocman S, Yoldas T, Kamanli A, et al: Auditory P300 event-related potentials and serotonin reuptake inhibitor treatment in patients with fibromyalgia. Ann Rheum Dis 2003; 62:551–555
11. Montoya P, Sitges C, Garcia-Herrera M, et al: Reduced brain habituation to somatosensory stimulation in patients with fibromyalgia. Arthritis Rheum 2006; 54:1995–2003
12. Geisser ME, Casey KL, Brucksch CB, et al: Perception of noxious and innocuous heat stimulation among healthy women and women with fibromyalgia: association with mood, somatic focus, and catastrophizing. Pain 2003; 102:243–250
13. Lautenbacher S, Rollman GB, McCain GA: Multi-method assessment of experimental and clinical pain in patients with fibromyalgia. Pain 1994; 59:45–53
14. Fields H: Depression and pain: a neurobiological model. Neuropsychiatry Neuropsychol Behav Neurol 1991; 4:83–92
15. Giesicke T, Gracely RH, Williams DA, et al: The relationship between depression, clinical pain, and experimental pain in a chronic-pain cohort. Arthritis Rheum 2005; 52:1577–1584
16. Sayar K, Barsky AJ, Gulec H: Does somatosensory amplification decrease with antidepressant treatment? Psychosomatics 2005; 46:340–344
17. Wolfe F, Hawley DJ: Evidence of disordered symptom appraisal in fibromyalgia: increased rates of reported comorbidity and comorbidity severity. Clin Exp Rheumatol 1999; 17:297–303
18. Bennett RM, Schein J, Kosinski MR, et al: Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen. Arthritis Rheum 2005; 53:519–527
19. Bergman S: Psychosocial aspects of chronic widespread pain and fibromyalgia. Disabil Rehabil 2005; 27:675–683
20. Reeves WC, Wagner D, Nisenbaum R, et al: Chronic fatigue syndrome: a clinically empirical approach to its definition and study. BMC Med 2005; 3:19
21. Melzack R: The Short-Form McGill Pain Questionnaire. Pain 1987; 30:191–197
22. Radloff L: The CES–D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977; 1:385–401
23. Berkman LF, Berkman CS, Kasl S, et al: Depressive symptoms in relation to physical health and functioning in the elderly. Am J Epidemiol 1986; 124:372–388
24. Geisser ME, Roth RS, Robinson ME: Assessing depression among persons with chronic pain, using the Center for Epidemiological Studies–Depression scale and the Beck Depression Inventory: a comparative analysis. Clin J Pain 1997; 13:163–170
25. Turk DC, Okifuji A: Detecting depression in chronic pain patients: adequacy of self-reports. Behav Res Ther 1994; 32:9–16
26. Smets EM, Garssen B, Bonke B, et al: The Multidimensional Fatigue Inventory (MFI): psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995; 39:315–325
27. Ware JE Jr: SF–36 Health Survey update. Spine 2000; 25:3130–3139
28. Ware JE Jr: Using generic measures of functional health and well-being to increase understanding of disease burden. Spine 2000; 25:1467
29. Petzke F, Khine A, Williams D, et al: Dolorimetry performed at three paired tender points highly predicts overall tenderness. J Rheumatol 2001; 28:2568–2569
30. Gracely RH, Lota L, Walter DJ, et al: A multiple random staircase method of psychophysical pain assessment. Pain 1988; 32:55–63
31. Gracely RH, Dubner R, McGrath PA: Narcotic analgesia: fentanyl reduces the intensity but not the unpleasantness of painful tooth pulp sensations. Science 1979; 203:1261–1263
32. Borg G: Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med 1970; 2:92–98
33. Lyden AK, Williams DA, Groner K, et al: Processing of sensory sensations associated with exercise and experimental pain in fibromyalgia. J Pain 2004; 5(3; suppl 1):37
34. Kerlinger FN, Pedhazer EJ: Multiple Regression in Behavioral Research: Explanation and Prediction. New York, Holt, Rinehart, and Winston, Inc, 1973, pp 281–333
35. Heim C, Wagner D, Maloney E, et al: Early adverse experience and risk for chronic fatigue syndrome: results from a population-based study. Arch Gen Psychiatry 2006; 63:1258–1266
36. Peters ML, Vlaeyen JWS, van Drunen C: Do fibromyalgia patients display hypervigilance for innocuous somatosensory stimuli? application of a body-scanning reaction time paradigm. Pain 2000; 86:283–292
37. Giesecke T, Gracely RH, Grant MAB, et al: Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum 2004; 50:613–623

38. Gracely RH, Petzke F, Park K, et al: Functional MRI evidence of augmented pain processing in fibromyalgia, Arthritis Rheum 2002; 46:1333–1343
39. Craig AD: Interoception: the sense of the physiological condition of the body. Curr Opin Neurol 2003; 13:500–505
40. Critchley HD, Wiens S, Rotshtein P, et al: Neural systems supporting interoceptive awareness. Nat Neurosci 2004; 7:189–195
41. Cook DB, Nagelkirk PR, Poluri A, et al: The influence of aerobic fitness and fibromyalgia on cardiorespiratory and perceptual responses to exercise in patients with chronic fatigue syndrome. Arthritis Rheum 2006; 54:3351–3362

Journal of Psychosomatic Research 57 (2004) 391–398

The effect of brief exercise cessation on pain, fatigue, and mood symptom development in healthy, fit individuals

Jennifer M. Glass[a,*], Angela K. Lyden[b], Frank Petzke[c], Phyllis Stein[d], Gail Whalen[e], Kirsten Ambrose[b], George Chrousos[f], Daniel J. Clauw[b]

[a] Department of Psychiatry and Institute for Social Research, University of Michigan, Ann Arbor, MI, USA
[b] Division of Rheumatology, Department of Medicine, University of Michigan, Ann Arbor, MI, USA
[c] Department of Anesthesiology, University of Cologne, Cologne, Germany
[d] Cardiovascular Division, Washington University, St. Louis, MO, USA
[e] Division of Rheumatology, Immunology, and Allergy, Georgetown University, Washington, DC, USA
[f] National Institute for Child Health & Development, NIH, Bethesda, MD, USA

Abstract

Objective: Abnormalities of the biological stress response (hypothalamic–pituitary–adrenal axis and the autonomic nervous system) have been identified in both fibromyalgia (FM) and chronic fatigue syndrome (CFS). Although these changes have been considered to be partly responsible for symptom expression, we examine an alternative hypothesis that these HPA and autonomic changes can be found in subsets of healthy individuals in the general population who may be at risk of developing these conditions. Exposure to ''stressors'' (e.g., infections, trauma, etc.) may lead to symptom expression (pain, fatigue, and other somatic symptoms) in part by precipitating lifestyle changes. In particular, we focus on the effect of deprivation of routine aerobic exercise on the development of somatic symptoms. **Methods:** Eighteen regularly exercising (≥ 4 h/week) asymptomatic, healthy adults refrained from physical activity for 1 week. We predicted that a subset of these individuals would develop symptoms of FM/CFS with exercise deprivation, and this manuscript focuses on the baseline HPA axis, immune, and autonomic function measures that may predict the development of symptoms. **Results:** Eight of the subjects reported a 10% increase in one or more symptoms (pain, fatigue, mood) after 1 week of exercise deprivation. These symptomatic subjects had lower HPA axis (baseline cortisol prior to VO2max testing), immune (NK cell responsiveness to venipuncture), and autonomic function (measured by heart rate variability) at baseline (prior to cessation of exercise) when compared to the subjects who did not develop symptoms. **Conclusions:** A subset of subjects developed symptoms of pain, fatigue, or mood changes after exercise deprivation. This cohort was different from the individuals who did not develop symptoms in baseline measures of HPA axis, immune, and autonomic function. We speculate that a subset of healthy individuals who have hypoactive function of the biological stress response systems unknowingly exercise regularly to augment the function of these systems and thus suppress symptoms. These individuals may be at risk for developing chronic multisymptom illnesses (CMIs) (e.g., FM or CFS among others) when a ''stressor'' leads to lifestyle changes that disrupt regular exercise.

Keywords: Fibromyalgia; Chronic fatigue syndrome; Exercise; Human stress response; Autonomic function; Pain; Fatigue

Introduction

Fibromyalgia (FM) and chronic fatigue syndrome (CFS) have been described in the medical literature for centuries, although these semantic terms are relatively new [1,2]. An umbrella term, chronic multisymptom illness (CMI), was coined to reflect this spectrum of disorders, which are characterized by otherwise unexplained widespread chronic pain, unremitting fatigue, and cognitive and mood complaints [3–5]. As with many illnesses, CMI may result when an individual who is genetically predisposed comes in contact with certain environmental exposures that can trigger the development of symptoms [6,7]. In this spectrum of illness, symptoms may develop acutely or subacutely after an individual is exposed to one or more ''stressors,'' including physical trauma (especially to the axial skeleton),

* Corresponding author. Institute for Social Research, University of Michigan, Room 5256, 426 Thompson Street, Ann Arbor, MI 48106-1248, USA. Tel.: +1-734-763-1512; fax: +1-734-764-3576.
E-mail address: jglass@umich.edu (J.M. Glass).

0022-3999/04/$ – see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.jpsychores.2004.04.002

infections or other immune stimulation, emotional distress (acute or chronic), and endocrine disorders [8–13]. In such instances, exposure to the stressor initiates the presentation of symptoms that can continue well after symptoms would normally remit.

One area of investigation in CMI has been the role and function of the "biological stress response," which allows the human body to respond and adapt to stimuli, both innocuous and otherwise. In both FM and CFS, abnormalities of the biological stress response have been identified in the hypothalamic–pituitary–adrenal axis, as well as the autonomic nervous system [3,14,15]. In general, individuals with these illnesses exhibit hypoactivity of both of these effector systems, especially when these systems are studied in the context of an acute experimental stressor [16–18]. In addition to these neurobiological findings, individuals with CMI also display aberrant sensory processing [19,20] and some experience psychiatric and psychological comorbidities.

A key issue in CMI is to identify what role these various neurobiological and psychological factors play in symptom expression. For each potential causative factor (e.g., HPA axis), there are several possible scenarios, i.e., the factor (1) is present before the onset of CMI (i.e., predisposing factor), (2) causes CMI, or (3) occurs as a consequence of CMI (epiphenomena caused by deconditioning, studying health care seeking participants, etc.). To determine which situation exists for a given factor, ideally longitudinal studies need to be performed to examine each factor from when individuals are asymptomatic, until they are symptomatic.

Such longitudinal mechanistic studies are very difficult to perform because only a small percentage of individuals who are exposed to any "stressor" will go on to develop symptoms. However, this study represents a first attempt at examining these factors longitudinally. We began by hypothesizing that there exist healthy individuals in the population who have a greater propensity toward the development of pain, fatigue, and other somatic symptoms and who avoid having such symptoms on a regular basis by exercising regularly. We felt that this "exercise deprivation" hypothesis was relevant to CMI for many reasons. First and foremost, aerobic exercise is amongst the most effective treatments for CMI [21,22]. Even in healthy individuals, routine aerobic exercise is associated with improved levels of fatigue, as well in reductions in overall pain threshold [23,24]. Very little work has been done on the effect of deprivation of regular exercise on specific symptoms, but there are some data suggesting that many healthy individuals report increased feelings of fatigue and irritability and increased numbers of somatic complaints when faced with a disruption to their regular exercise program [25]. Since exercise is known to lead to improvements in pain sensitivity and changes in immune, HPA, and autonomic function, it is equally plausible that reduced exercise would also affect these physiologic parameters [26–28]. Finally, we have noted that many CMI patients anecdotally report that they were very active prior to the development of their illness. This makes it plausible to hypothesize that the "stressors" that appear to be capable of triggering these conditions such as infections, trauma, etc., might do so indirectly—by causing individuals to stop regular exercise, thus leading to the development of symptoms.

To test these hypotheses, we asked healthy active adults to refrain from physical activity for 1 week. At baseline, we measured pain, fatigue, and mood symptoms as well as HPA axis, immune, and autonomic function. This manuscript focuses on the baseline physiologic parameters that predicted the development of CMI symptoms.

Methods

Subjects

Asymptomatic, healthy active adults who reported performing more than 4 h of aerobic activity per week were recruited to participate in this study. Individuals with any chronic medical conditions or taking any medications regularly (except for birth control pills or as-needed analgesics) were excluded from participating. Each volunteer read and signed an informed consent document that had been approved by the Institutional Review Board for human subjects at Georgetown University Medical Center.

Eighteen subjects, 7 males and 11 females, participated in the study. The mean age of the participants was 25.24 ±3.25 (yrs). They reported performing an average of 5.73 ±2.20 h of exercise weekly, with a range of 4–11.

Study design

The study design was to administer an identical series of questionnaires and tests while participants were exercising regularly (baseline) and then after 1 week of exercise cessation. A 7-day hiatus was chosen largely for pragmatic reasons, in that this was hypothesized to be the amount of time that most individuals would be willing to eschew their regular exercise. Baseline data were collected in the morning of the day following their last day of exercise. The second set of studies was performed in the morning on the 7th day of exercise deprivation. Subjects reported to the lab at 0730, at which time an intravenous catheter was inserted. Subjects rested in a semirecumbent position for at least 20 min prior to baseline blood sampling. After the tenderpoint and dolorimeter exams, the exercise test was commenced at 0830.

Self-report measures

Subjects completed self-report questionnaires at baseline and on the last day before their return to exercise. These inventories were chosen to capture symptomatology in three domains associated with CMI: pain, fatigue, and mood. The short-form McGill Pain Questionnaire was used to assess global and regional pain presence and severity [29]. The

Multidimensional Fatigue Inventory was used to quantify different facets of fatigue [30]. The Beck Depression Inventory and Speilberger State-Trait Anxiety Inventory were used to assess mood and affect [31,32].

Tenderness

Each subject underwent both a manual tenderpoint exam and a dolorimeter exam to evaluate whole body tenderness [33,34]. The manual tenderpoint exam was performed using standardized methodology with digital pressure of approximately 4 kg applied to 11 (9 "tender" and 2 "control" points) designated bilateral musculotendinous sites. Subjects were asked to indicate if they experienced tenderness at a particular site, thus giving a dichotomous "yes/no" response for each anatomical site. A dolorimeter exam was performed with a pressure algometer (Chantillon, Kew Gardens, NJ) at these same 22 points. In this testing, the subject was asked when they began to experience pain and when it became intolerable. In this manner, both a pain threshold and tolerance were recorded for each subject.

Autonomic function

Autonomic dysfunction has been demonstrated in CMI patients [35,36]. In particular, analyses of heart rate variability have demonstrated abnormal ratios of sympathetic–parasympathetic balance.[37–39] Heart rate variability represents the beat-to-beat variations in consecutive R–R intervals. Fluctuations over time in these intervals are mediated by autonomic inputs to the sinus node, and measures of this heart rate variability represent a surrogate measure of autonomic nervous system modulation. Subjects reported to the lab on the morning prior to testing to receive their Holter monitor. Each subject wore a Holter monitor (Space Labs, Redmond, VA) for the 24 h preceding and including the testing periods at baseline and postexercise cessation. For each recording, we evaluated the HRV across the different domains of the spectral density curve (Frequency Domain Analysis), including the high, low, very low frequencies, as well as the high to low (HF–LF) ratio. Standard convention suggests that the high frequency domain (HF) largely reflects vagal contribution to the beat-to-beat variations in heart rate [40,41]. It is the highest frequency band quantified and reflects primarily respiration-mediated HRV in the 0.15 to 0.4-Hz band. The low frequency band (LF) is thought to be modulated by both the sympathetic and parasympathetic nervous systems. It is measured between 0.04 and 0.15 Hz [40]. Even slower modulations of heart rate are reflected in the very low frequency domain (VLF), 0.0033–0.04 Hz. VLF may represent the influence of the peripheral vasomotor and rennin–angiotensin systems [42]. The remainder of the power spectrum is subsumed by the ultra low frequency domain (ULF), which reflects all variance below 0.0033 Hz, and consists of mainly circadian rhythms. All of these indices together represent the total power (TP), which is the sum of all the variance in the heart period signal. The HF–LF is useful to evaluate fluctuations in the balance between the sympathetic and parasympathetic nervous systems.

Aerobic capacity

Subjects completed a treadmill VO2 test to volitional fatigue at baseline and postexercise cessation. The test was used not only to evaluate aerobic capacity, but to serve as a physiological stressor as well. After a 5-min running warm up on the treadmill, speed was increased 1 mile an hour faster; then every 2 min, the grade was increased in 2% increments. Heart rate was continuously monitored via the Quinton 4500 Stress Test Monitoring System (Quinton Instruments, Seattle, WA). Ratings of perceived exertion were recorded during the final 15 s of each stage. Expired air was collected and analyzed using a Marquette Metabolic Gas Analyzer 1100 (Marquette Electronics, Jupiter, FL) during the final min of each stage. Subjects were permitted a brief active recovery, after which they remained in a semirecumbent position for the rest of the testing period.

Immune function

Recent evidence suggests that immune function, NK cell activity in particular, may be a surrogate index of the function of various components of the nervous system, especially the sympathetic nervous system [43,44]. Stimulation of these receptors affects lymphocyte traffic, circulation and proliferation, and modulates cytokine production [45]. Immune dysfunction has been reported most consistently in CFS patients, who show chronic immune activation [46–49] and other abnormalities including low NK cell activity [50,51]. Similar results have been found in other CMI illnesses [52–55].

At Time 0, an intravenous catheter was inserted and we drew a blood sample into EDTA-prepared tubes. After a 20-min rest period, a second sample was drawn, which was considered "baseline" since previous work by our group and others has demonstrated that the cell trafficking changes due to humoral factors return to baseline by this time [56]. Immune studies were performed immediately on all samples. A CBC with differential was performed to allow for calculation of absolute cell counts. The NK cytotoxicity was performed according to standard 51-Chromium (51Cr) release microtoxicity protocols [57]. Percent cytotoxicity (percent 51Cr) was determined and then subsequently used to calculate lytic units (LU), the number of effector cells required to lyse 20% of the target cells.

HPA axis function

Patients with CMI display a number of abnormalities in neuroendocrine function, especially involving the HPA axis [3,58] that suggest a blunting of various components

[59,60]. We measured plasma cortisol and ACTH at several time points during the exercise stressor. Samples were collected from an indwelling intravenous catheter immediately postintravenous insertion, 20 min postintravenous insertion, pre-VO2 max testing (after a 5-min warm up on the treadmill), at peak exercise, 20 min postexercise, and 60 min postexercise. The samples were processed and stored in a −70 °C freezer until later analysis for cortisol and ACTH analysis. Cortisol and ACTH were analyzed by an independent laboratory using commercially available kits.

Statistics

Statistical analysis was performed using SPSS v9.0 software (Chicago, IL). For individual data, a 10% change in any symptom measure over 1 week was a priori deemed to be clinically significant. Independent *t* tests were used to evaluate potential differences between subject groups (ASX vs. SX). Significance was defined as $P < .05$.

Results

Symptom development

Following 1 week of exercise cessation, 8 of the 18 participants had increased symptoms. This was defined as a worsening of 10% or more in baseline measures of clinical (McGill) or evoked pain (dolorimeter), global fatigue (Multidimensional Fatigue Inventory), or mood (Beck Depression or Speilberger Anxiety inventories). To assign subjects to either the asymptomatic or the symptomatic group, each subject was given a score (−1 = improvement, 0 = no change, and 1 = worsening) for each of the three symptom domains (pain, fatigue, and mood). These scores were added; subjects with a score of 1 or higher were placed in the symptomatic group and subjects with a score of 0 or less were placed in the asymptomatic group. Five individuals had a worsening of fatigue, three had an increase in preexisting pain or an increase in tenderness, and three had a significant increase in depressive or anxiety symptoms. Differences in pre- and postexercise deprivation scores are shown in Table 1 for each subject along with their classification as symptomatic or asymptomatic. The two groups (ASX vs. SX) were similar with respect to age (25 vs. 26.3 years), mean hour per week devoted to aerobic exercise (4.35 vs. 6.17), and aerobic capacity (VO2max: 50.1 vs. 53.1). The VO2max scores indicated that most of our subjects had above average aerobic capacity (15 subjects were at or above the 85th percentile, one subject was at the 60th percentile, and one was at the 50th percentile).

Physiological changes

Mean group effects on each of the physiological measures were calculated and are described below. Individual

Table 1
Individual exercise deprivation difference (post−pre) scores and symptom categories

	Post- to predifference scores									
	Fatigue		Mood		Pain		Categories			
Case No.	MFI-G	MFI-P	BDI	STAI	McG	TPTh[a]	Fatigue	Mood	Pain	Sum
ASX										
1	3	−2	−3	2	1.3	0.1	0	0	0	0
2	2	−3	−1	−5	1.3	−0.2	0	−1	1	0
3	−1	0	0	1	0	0.4	0	0	−1	−1
4	8	6	0	−11	2.5	0.5	1	−1	0	0
5	2	2	−2	−6	–	1.3	1	−1	−1	−1
6	−2	0	−1	−1	0	0.3	−1	0	0	−1
7	0	0	−6	7	0	0	0	0	0	0
8	0	2	1	−9	0	−0.1	1	−1	0	0
9	2	0	0	1	0	0	0	0	0	0
10	−2	4	1	−2	0	−0.1	0	0	0	0
SX										
11	−2	0	0	0	0	−1.0	0	0	1	1
12	3	1	3	6	−1.5	−0.5	1	1	0	2
13	3	0	5	4	−1.9	0.1	1	1	−1	1
14	2	1	0	2	0	0.2	1	0	0	1
15	3	6	4	1	1.5	−0.3	1	0	1	2
16	0	1	1	7	0	0.0	1	0	0	1
17	−1	−1	1	−2	0	−0.4	0	1	0	1
18	−3	1	−1	−4	0.1	0.1	0	0	1	1

Note: MFI-G = Multiple Fatigue Inventory—General; MFI-P = Multiple Fatigue Inventory—Physical; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Index; McG = McGill current pain severity; TPTh = average dolorimeter tenderpoint threshold.

[a] Positive difference in threshold indicates improvement.

Table 2
Individual subject data and group means for physiological measures

Case No.	TP ($m \cdot s^2$)	HF ($m \cdot s^2$)	LF ($m \cdot s^2$)	VLF ($m \cdot s^2$)	LU Time 0	LU baseline	Cortisol (μg/dl) baseline	ACTH baseline
ASX								
1	–	–	–	–	54.00	39.00	39.33	0.30
2	–	–	–	–	31.00	27.00	24.67	0.21
3	10511.32	4934.79	2414.06	2934.83	80.00	49.00	36.23	0.46
4	–	–	–	–	40.00	25.00	32.86	0.15
5	18955.17	8255.17	4385.22	2903.86	217.00	158.00	44.86	0.37
6	–	–	–	–	15.00	14.00	38.55	0.33
7	14343.41	8462.77	3155.12	3849.77	182.00	58.00	55.43	0.20
8	–	–	–	–	47.00	36.00	42.57	0.34
9	23535.65	12899.84	3981.72	2565.97	40.00	52.00	27.24	0.19
10	2298.75	1035.53	1021.72	268.63	34.00	32.00	–	–
Means	13929	7116	2992	2506	74.00	49.00	37.97	0.28
SX								
11	–	–	–	–	44.00	47.00	15.87	0.64
12	6816.53	4283.17	1037.48	1072.39	124.00	98.00	15.55	0.20
13	13787.10	7414.38	2275.40	1967.81	159.00	162.00	30.35	0.20
14	–	–	–	–	198.00	207.00	18.58	0.25
15	6034.44	6454.63	829.96	495.15	42.00	69.00	33.91	0.12
16	3582.73	3110.92	690.55	214.24	241.00	231.00	26.91	0.19
17	13055.96	6822.70	2488.69	1948.81	132.00	153.00	47.33	0.31
18	2697.92	1383.52	771.74	168.43	20.00	31.00	30.83	0.20
Means	7662	4912	1349	978	124.00	120.00	27.42	0.26

Note: ASX = asymptomatic; SX = symptomatic; TP = total power (heart rate variability); HF = high frequency heart rate variability; LF = low frequency heart rate variability; VLF = very low frequency heart rate variability; LU = lytic units; ACTH = adrenocorticotropic hormone; Time 0 = time of venipuncture; Baseline = 20 min semirecumbent rest period after venipuncture.

subject data as well as group means for these measures are shown in Table 2.

Immune function

As expected, NK cell function significantly increased from resting to peak exercise and returned to resting levels by one h of recovery, both before and after exercise cessation. Prior to exercise deprivation, the SX group displayed higher baseline levels of LU [$t(16) = -2.76$, $P = .014$]. In addition, the ASX group displayed a marked increase in number and activity of LU [49 ± 40 to 74 ± 68 LU, $t(9) = 1.98$, $P = .079$] in response to the stress of venipuncture relative to baseline, while the SX subjects failed to show any such response [124 ± 74.54 to 120 ± 79 LU, $t(7) = -0.798$, $P = .45$]. This attenuated NK responsiveness to the stress of venipuncture was very similar to findings our group had previously noted in FM subjects [56]. It is possible that the low responsiveness in the SX group may be due to a chronically high level of NK activity, as evidenced by the significant baseline differences between the groups.

Heart rate variability

Seven subjects (five from the ASX group and two from the SX group) had missing data for the heart rate variability analyses due to equipment failure. Because of the exploratory nature of this study, we simply ignored the missing data. At baseline, there was a trend for diminished HRV in all areas of the power spectral density curve for the SX group compared to the ASX group. These differences reached statistical significance in both the LF [$t(9) = 2.50$, $P = .033$ and VLF ($t(9) = 2.30$, $P = .045$] portions of the spectra, which are rough correlates of sympathetic activity.

HPA axis markers

At baseline, the SX subjects had a significantly lower baseline cortisol (drawn prior to the beginning of the VO2max testing) level than did the ASX group [27.42 ± 3.81 vs. 37.97 ± 3.11, $t(15) = 2.166$, $P < .05$]. There were no significant differences between the two groups in ACTH at any time point.

Discussion

Our hypothesis that some individuals would develop somatic symptoms similar to those seen in CMI after cessation of exercise was supported. Eight of 17 subjects went on to develop somatic symptoms following 1 week of exercise cessation. Fatigue seemed to be the most prominent symptom, followed by increased reported pain and mood disturbances. These are the first studies we are aware of to look so globally at the effects of exercise cessation. Previous studies have primarily dealt with mood changes [25] or have characterized metabolic or cardiovascular adaptations [61].

For example, alterations in nociceptive tolerance (tenderness) with exercise cessation have not previously been considered. We found that five subjects experienced a 10% increase in tenderness over the course of a week of

exercise deprivation. Whether tenderness would continue to increase over a protracted period of detraining is unknown, although we speculate that if faced with a stressor of sufficient intensity and duration to disrupt their routine, these particular individuals would indeed begin to develop increasing levels of pain sensitivity. Alternatively, a group of subjects with higher baseline levels of tenderness may exhibit a more pronounced tendency toward increased tenderness following seven days of exercise cessation.

Mood changes or perceived cognitive difficulties were not pronounced in our sample. The study design may have influenced these particular parameters. Questionnaires were distributed at the beginning (Day 1) and the end (Day 7) of the 7-day exercise cessation period, with the first possible day of return-to-exercise being the afternoon of Day 7 (after testing). It is possible that the stable responses to both the BDI and STAI may reflect an anticipatory response to the prospect of returning to exercise. Mood assessments throughout the week may have resulted in better capture of any changes in mood and affect.

Arguably, the most interesting results of this study were that the subjects who developed symptoms after exercise cessation had different baseline HPA, autonomic, and immune function measures. In general, those subjects who went on to develop symptoms appear to have baseline physiologic characteristics similar to those individuals with established cases of CMI such as FM and CFS, although admittedly both hypo- and hyperactivity of the HPA and autonomic systems have been noted in some studies of FM and CFS [3,14,62–64]. What is perhaps more important than the actual abnormality (i.e., hypo or hyper) is that the individuals in the cohort that went on to develop symptoms with exercise deprivation had different baseline HPA and autonomic and sensory processing function. Thus, these data are the first we know of to support the notion that some of these physiologic changes that have been identified in CMI may antedate the development of symptoms and may serve as a diathesis that contributes to the development of symptoms.

Although further research is necessary to replicate these results, this study is important because it represents a prospective study of CMI development and suggests a way that triggers such as physical or emotional trauma might lead to the development of CMI in susceptible individuals. Although preliminary, these data suggest that some of the differences seen in the stress responsiveness in CMI may actually antedate the development of symptoms and provide a possible explanation for why so many different types of stressors (e.g., viral, physical trauma, emotional stress) can trigger CMI: these many types of stressors can precipitate a change in lifestyle (e.g., cessation of exercise, disruption of sleep) for a prolonged period. Early studies by Moldofsky and Scarisbrick [65] suggested that sleep deprivation may contribute to FM-like symptoms, and future studies should examine how exercise and sleep deprivation may interact to cause such changes.

Acknowledgments

This study was supported in part by Department of the Army grant DAMD 17-002-0018.

References

[1] Yunus MB, Holt GS, Masi AT, Aldag JC. Fibromyalgia syndrome among the elderly. Comparison with younger patients. J Am Geriatr Soc 1988;36(11):987–95.
[2] Turner R, Le Bihan D, Moonen CTW, Frank J. Echo-planar imaging of deoxygenation episodes in cat brain at 2T;1991.
[3] Crofford LJ, Demitrack MA. Evidence that abnormalities of central neurohormonal systems are key to understanding fibromyalgia and chronic fatigue syndrome. Rheum Dis Clin North Am 1996;22(2): 267–84.
[4] Nisenbaum R, Reyes M, Mawle AC, Reeves WC. Factor analysis of unexplained severe fatigue and interrelated symptoms: overlap with criteria for chronic fatigue syndrome. Am J Epidemiol 7-1- 1998; 148(1):72–7.
[5] King SJ, Wessel J, Bhambhani Y, Sholter D, Maksymowych W. Predictors of success of intervention programs for persons with fibromyalgia. J Rheumatol 2002;29(5):1034–40.
[6] Buxton J, White M, Osoba D. Patients' experiences using a computerized program with a touch-sensitive video monitor for the assessment of health-related quality of life. Qual Life Res 1998;7(6):513–9.
[7] Fields HL. Core curriculum for professional education in pain. Seattle: IASP Publications, 1991.
[8] Buskila D, Neumann L, Vaisberg G, Alkalay D, Wolfe F. Increased rates of fibromyalgia following cervical spine injury. A controlled study of 161 cases of traumatic injury. Arthritis Rheum 1997;40(3): 446–52.
[9] Waylonis GW, Perkins RH. Post-traumatic fibromyalgia. A long-term follow-up. Am J Phys Med Rehabil 1994;73(6):403–12.
[10] Goldenberg DL. Fibromyalgia and its relation to chronic fatigue syndrome, viral illness and immune abnormalities. J Rheumatol Suppl 1989;19:91–3.
[11] Culclasure TF, Enzenauer RJ, West SG. Post-traumatic stress disorder presenting as fibromyalgia. Am J Med May 1993;94:548–9.
[12] Hazlett RL, Haynes SN. Fibromyalgia: a time-series analysis of the stressor-physical symptom association. J Behav Med 1993;15: 541–58 (December 1992).
[13] Dailey PA, Bishop GD, Russell IJ, Fletcher EM. Psychological stress and the fibrositis/fibromyalgia syndrome. J Rheumatol 1993;17: 1380–5 (October 1990).
[14] Demitrack MA, Dale JK, Straus SE, Laue L, Listwak SJ, Kruesi MJ, Chrousos GP, Gold PW. Evidence for impaired activation of the hypothalamic–pituitary–adrenal axis in patients with chronic fatigue syndrome. J Clin Endocrinol Metab 1994;73:1224–34 (December 1991).
[15] Demitrack MA, Dale JK, Straus SE, Laue L, Listwak SJ, Kruesi MJ, Chrousos GP, Gold PW. Evidence for impaired activation of the hypothalamic–pituitary–adrenal axis in patients with chronic fatigue syndrome. J Clin Endocrinol Metab 1991;73(6):1224–34.
[16] Crofford LJ, Engleberg NC, Demitrack MA. Neurohormonal perturbations in fibromyalgia. Bailliere's Clin Rheumatol 1996;10(2):365–78.
[17] Samborski W, Stratz T, Kretzmann WM, Mennet P, Muller W. Comparative studies of the incidence of vegetative and functional disorders in backache and generalized tendomyopathies. Z Rheumatol 1991;50(6):378–81.
[18] Crofford LJ, Pillemer SR, Kalogeras KT, Cash JM, Michelson D, Kling MA, Sternberg EM, Gold PW, Chrousos GP, Wilder RL. Hypothalamic–pituitary–adrenal axis perturbations in patients with fibromyalgia. Arthritis Rheum 1994;37(11):1583–92.

[19] Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46(5):1333–43.
[20] Yunus MB. Towards a model of pathophysiology of fibromyalgia: aberrant central pain mechanisms with peripheral modulation (editorial). J Rheumatol 1992;19(6):846–50.
[21] Busch A, Schachter CL, Peloso PM, Bombardier C. Exercise for treating fibromyalgia syndrome. Cochrane Database Syst Rev. 2002;(3):CD003786.
[22] Goudsmit EM. Measuring the quality of trials of treatments for chronic fatigue syndrome. JAMA 2001;286(24):3078–9 (December 26).
[23] Guieu R, Blin O, Pouget J, Serratrice G. Nociceptive threshold and physical activity. Can J Neurol Sci 1992;19(1):69–71.
[24] Janal MN, Colt EW, Clark WC, Glusman M. Pain sensitivity, mood and plasma endocrine levels in man following long-distance running: effects of naloxone. Pain 1984;19(1):13–25.
[25] Mondin GW, Morgan WP, Piering PN, Stegner AJ, Stotesbery CL, Trine MR, Wu MY. Psychological consequences of exercise deprivation in habitual exercisers. Med Sci Sports Exerc 1996;28(9): 1199–203.
[26] Luger A, Deuster PA, Kyle SB, Gallucci WT, Montgomery LC, Gold PW, Loriaux DL, Chrousos G. Acute hypothalamic–pitutitary–adrenal response to the stress of treadmill exercise: physiological adaptations to physical training. N Engl J Med 1987;316(21): 1309–15.
[27] Petrides JS, Mueller GP, Chrousos G, Kalogeras K, Deuster PA. Exercise-induced activation of the hypothalamic–pituitary–adrenal (HPA) axis: differential sensitivity to glucocorticoid suppression. J Clin Endocrinol Metab 1994;79:377–83.
[28] Granges G, Littlejohn GO. A comparative study of clinical signs in fibromyalgia/fibrositis syndrome, healthy and exercising subjects. J Rheumatol 1993;20:344–51 (February 1993).
[29] Melzack R. The short-form McGill pain questionnaire. Pain 1987;30 (2):191–7.
[30] Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39(3):315–25.
[31] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:53–63 (June).
[32] Palo Alto, CA Consulting Psychologists, 1983. 1996.
[33] Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee (see comments). Arthritis Rheum 1993;33:160–72 (February 1990).
[34] Sorensen J, Graven-Nielsen T, Henriksson KG, Bengtsson M, Arendt-Nielsen L. Hyperexcitability in fibromyalgia. J Rheumatol 1998;25: 152–5.
[35] Radulovic D, Barbey JT, Katz P, Baraniuk J, Clauw DJ. Tilt table testing as a measure of dysautonomia in fibromyalgia (FM). Arthritis Rheum 1995;38(6):R25.
[36] Soetekouw PM, Lenders JW, Bleijenberg G, Thien T, van der Meer JW. Autonomic function in patients with chronic fatigue syndrome. Clin Auton Res 1999;9(6):334–40.
[37] Clauw DJ, Heshmat Y, Groner K, Gondy G, Barbey JT. Heart rate variability as a measure of autonomic function in patients with fibromyalgia. Arthritis Rheum 1996;39(Suppl 9):S276.
[38] Clauw DJ, Radulovic D, Heshmat Y, Barbey JT. Heart rate variability as a measure of autonomic function in patients with fibromyalgia (FM) and chronic fatigue syndrome (CFS). Arthritis Rheum 1995; 38(Suppl 6):R25.
[39] Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D. Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability (see comments). Semin Arthritis Rheum 2000;29(4):217–27.
[40] Gr:onblad M, Nykanen J, Konttinen Y, Jarvinen E, Helve T. Effect of zopiclone on sleep quality, morning stiffness, widespread tenderness and pain and general discomfort in primary fibromyalgia patients. A double-blind randomized trial. Clin Rheumatol 1993;12:186–91 (June 1993).
[41] Barsky AJ, Goodson JD, Lane RS, Cleary PD. The amplification of somatic symptoms. Psychosom Med 1988;50(5):510–9.
[42] Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213:220–2.
[43] Schedlowski M, Jacobs R, Stratmann G, Richter S, Hadicke A, Tewes U, Wagner TOF, Schmidt RE. Changes of natural killer cells during acute psychological stress. J Clin Immunol 1993;13(2):119–26.
[44] Tonnesen E, Christensen NJ, Brinklov MM. Natural killer cell activity during cortisol and adrenaline infusion in healthy volunteers. Eur J Clin Invest 1987;17:497–503.
[45] Chrousos GP. The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. N Engl J Med 1995;332(20):1351–62 (May 18).
[46] Whiteside TL, Friberg D. Natural killer cells and natural killer cell activity in chronic fatigue syndrome. Am J Med 1998;105(3A):27S–34S (September 28).
[47] Bates DW, Buchwald D, Lee J, Kith P, Doolittle T, Rutherford C, Churchill WH, Schur PH, Wener M, Wybenga D. Clinical laboratory test findings in patients with chronic fatigue syndrome. Arch Intern Med 1995;155(1):97–103 (January 9).
[48] Buchwald D, Wener MH, Pearlman T, Kith P. Markers of inflammation and immune activation in chronic fatigue and chronic fatigue syndrome. J Rheumatol 1997;24(2):372–6.
[49] Klimas NG, Salvato FR, Morgan R, Fletcher MA. Immunologic abnormalities in chronic fatigue syndrome. J Clin Microbiol 1990;28(6): 1403–10.
[50] Barker E, Fujimura SF, Fadem MB, Landay AL, Levy JA. Immunologic abnormalities associated with chronic fatigue syndrome. Clin Infect Dis 1994;18(Suppl 1):S136–41.
[51] Buchwald D, Komaroff AL. Review of laboratory findings for patients with chronic fatigue syndrome. Rev Infect Dis 1991;13(Suppl 1): S12–8.
[52] Bell IR, Baldwin CM, Schwartz GE. Illness from low levels of environmental chemicals: relevance to chronic fatigue syndrome and fibromyalgia. Am J Med 1998;105(3A):74S–82S (September 28).
[53] Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 1997;4(3):134–53.
[54] Clauw DJ, Whalen G, Groner K, Lyden A, Katz P, Cupps T. Is autonomic dysfunction the cause of ‘‘immune dysfunction’’ in fibromyalgia (FM) and Chronic Fatigue Syndrome (CFS)? Arthritis Rheum 1997;40(Suppl 9):S42.
[55] Lekander M, Fredrikson M, Wik G. Neuroimmune relations in patients with fibromyalgia: a positron emission tomography study. Neurosci Lett 2000;282(3):193–6 (March 24).
[56] Clauw DJ, Whalen G, Groner K, Lyden A, Katz P, Cupps T. Is autonomic dysfunction the cause of ‘‘immune dysfunction’’ in fibromyalgia (FM) and Chronic Fatigue Syndrome (CFS)? Arthritis Rheum 1997;40(Suppl 9):S42.
[57] Cell Immunol. vol. 120,1989.
[58] Demitrack MA. Chronic fatigue syndrome: a disease of the hypothalamic–pituitary–adrenal axis? (editorial). Ann Med 1994;26(1):1–5.
[59] Catley D, Kaell AT, Kirschbaum C, Stone AA. A naturalistic evaluation of cortisol secretion in persons with fibromyalgia and rheumatoid arthritis. Arthritis Care Res 2000;13(1):51–61.
[60] Cofford LJ, Engleberg NC, Brucksch C, Eisner S, Papadopoulos E, Krstov M, Korszun A, Young EA, Demitrack MA. Analysis of circadian plasma ACTH and cortisol levels in patients with fibromyalgia (FM) and Chronic Fatigue Syndrome (CFS). Arthritis Rheum 1996; 39(Suppl 9):1487.
[61] Coyle EF, Martin WH, Sinacore DR, Joyner MJ, Hagberg JM, Holloszy JO. Time course of loss of adaptations after stopping prolonged intense endurance training. J Appl Physiol 1984;57(6):1857–64.

[62] Levine PH, Whiteside TL, Friberg D, Bryant J, Colclough G, Herberman RB. Dysfunction of natural killer activity in a family with chronic fatigue syndrome. Clin Immunol Immunopathol 1998;88(1): 96–104.

[63] Martinez-Lavin M, Hermosillo AG. Autonomic nervous system dysfunction may explain the multisystem features of fibromyalgia. (editorial; comment). Semin Arthritis Rheum 2000;29(4):197–9.

[64] Crofford LJ, Demitrack MA. Evidence that abnormalities of central neurohormonal systems are key to understanding fibromyalgia and chronic fatigue syndrome. Rheum Dis Clin North Am 1996;22(2): 267–84.

[65] Moldofsky H, Scarisbrick P. Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. Psychosom Med 1976;38:35–44.

DOI: 10.1093/brain/awh098 *Brain* (2004), **127,** 835–843

Pain catastrophizing and neural responses to pain among persons with fibromyalgia

R. H. Gracely,[1] M. E. Geisser,[2] T. Giesecke,[3] M. A. B. Grant,[1] F. Petzke,[3] D. A. Williams[1] and D. J. Clauw[1]

[1]*Chronic Pain and Fatigue Research Center, Department of Internal Medicine, Division of Rheumatology,* [2]*Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, MI, USA and* [3]*Department of Anesthesiology and Intensive Care, University of Cologne, Cologne, Germany*

Correspondence to: Daniel J. Clauw, MD, University of Michigan Health System, Department of Internal Medicine, Division of Rheumatology, Chronic Pain and Fatigue Research Center, 24 Frank Lloyd Wright Drive, PO Box 385, Ann Arbor, MI 48106, USA
E-mail: dclauw@med.umich.edu

Summary

Pain catastrophizing, or characterizations of pain as awful, horrible and unbearable, is increasingly being recognized as an important factor in the experience of pain. The purpose of this investigation was to examine the association between catastrophizing, as measured by the Coping Strategies Questionnaire Catastrophizing Subscale, and brain responses to blunt pressure assessed by functional MRI among 29 subjects with fibromyalgia. Since catastrophizing has been suggested to augment pain perception through enhanced attention to painful stimuli, and heightened emotional responses to pain, we hypothesized that catastrophizing would be positively associated with activation in structures believed to be involved in these aspects of pain processing. As catastrophizing is also strongly associated with depression, the influence of depressive symptomatology was statistically removed. Residual scores of catastrophizing controlling for depressive symptomatology were significantly associated with increased activity in the ipsilateral claustrum ($r = 0.51$, $P < 0.05$), cerebellum ($r = 0.43$, $P < 0.05$), dorsolateral prefrontal cortex ($r = 0.47$, $P < 0.05$), and parietal cortex ($r = 0.41$, $P < 0.05$), and in the contralateral dorsal anterior cingulate gyrus (ACC; $r = 0.43$, $P < 0.05$), dorsolateral prefrontal cortex ($r = 0.41$, $P < 0.05$), medial frontal cortex ($r = 0.40$, $P < 0.05$) and lentiform nuclei ($r = 0.40$, $P < 0.05$). Analysis of subjects classified as high or low catastrophizers, based on a median split of residual catastrophizing scores, showed that both groups displayed significant increases in ipsilateral secondary somatosensory cortex (SII), although the magnitude of activation was twice as large among high catastrophizers. Both groups also had significant activations in contralateral insula, SII, primary somatosensory cortex (SI), inferior parietal lobule and thalamus. High catastrophizers displayed unique activation in the contralateral anterior ACC, and the contralateral and ipsilateral lentiform. Both groups also displayed significant ipsilateral activation in SI, anterior and posterior cerebellum, posterior cingulate gyrus, and superior and inferior frontal gyrus. These findings suggest that pain catastrophizing, independent of the influence of depression, is significantly associated with increased activity in brain areas related to anticipation of pain (medial frontal cortex, cerebellum), attention to pain (dorsal ACC, dorsolateral prefrontal cortex), emotional aspects of pain (claustrum, closely connected to amygdala) and motor control. These results support the hypothesis that catastrophizing influences pain perception through altering attention and anticipation, and heightening emotional responses to pain. Activation associated with catastrophizing in motor areas of the brain may reflect expressive responses to pain that are associated with greater pain catastrophizing.

Keywords: catastrophizing; functional neuroimaging; fibromyalgia; pain modulation

Abbreviations: ACC = anterior cingulate cortex; BA = Brodmann area; fMRI = funtional MRI; IPL = inferior parietal lobule; MPQ = McGill Pain Questionnaire; SI = primary somatosensory cortex; SII = secondary somatosensory cortex; VAS = visual analogue scale

Received August 18, 2003. Revised November 25, 2003. Accepted December 9, 2003 Advance Access publication February 11, 2004

Introduction

The experience of pain is a multidimensional phenomenon that is influenced by multiple factors, such as affect, previous experience and cultural beliefs, in addition to sensory input (Melzack and Wall, 1982). Among persons with chronic pain, psychosocial factors may play a significant role in the development and maintenance of the disorder (Bigos *et al*., 1992; Burton *et al*., 1995; Gatchel *et al*., 1995). Psychosocial factors that probably influence the experience of pain include cognitions (i.e. thoughts, beliefs and appraisals), coping responses and social environmental variables (Jensen *et al*., 2002).

Pain catastrophizing, or responses to pain that characterize it as being awful, horrible and unbearable, is increasingly recognized as an extremely important contributor to the experience of pain. Early studies on catastrophizing suggested that these maladaptive responses to pain mirrored responses typically observed in persons with depression and proposed that catastrophizing was merely a symptom of depression rather than a separate entity (Rosenstiel and Keefe, 1983; Sullivan and D'Eon, 1990). Later studies, however, have found catastrophizing to be significantly associated with pain and pain-related disability independent of the influence of depression and negative affect (Keefe *et al*., 1989, 1990; Geisser *et al*., 1994, 2003; Geisser and Roth, 1998; Sullivan *et al*., 1998). These studies provide strong support for the notion that catastrophizing plays an important role in the experience of chronic pain independent of its observed relationship to depression. The influence of catastrophizing on pain can be substantial. Burton *et al*. (1995) observed that catastrophizing alone accounted for 47% of the variance in predicting the development of chronic pain from an episode of acute pain.

Although the mechanisms by which catastrophizing influences the experience of pain are not known (Sullivan *et al*., 2001), one hypothesis is that pain catastrophizing influences the attentional focus on painful or potentially painful events. Persons who catastrophize have difficulty shifting their focus of attention away from painful or threatening stimuli, and attach more threat or harm to non-painful stimuli (Crombez *et al*., 1998, 2002; Peters *et al*., 2000). These studies suggest that catastrophizing increases pain-related fear, which in turn increases attention to the stimulus. Thus, in addition to intensity, the threat value of the stimulus may be an important mediator of altered pain perception. There is also evidence that catastrophizing is positively associated with affective pain ratings, which in turn may lead to higher overall evaluations of the experience of pain (Geisser *et al*., 1994).

Despite the proposed importance of cognitive and emotional factors in the experience of pain, few studies have assessed the association between these factors and the neurophysiolgical mechanisms involved in pain processing. Cognitive factors associated with pain, such as catastrophizing, should be observable through methods such as functional brain imaging. Attention biases towards painful stimuli have been shown to produce unique brain activation independent of painful stimulation. For example, Brooks *et al*. (2002) found a unique pattern of insula activation when subjects shifted their attention away from the stimulated hand. Similarly, Ploghaus *et al*. (1999) found a distinct pattern of activation in the insular cortex, medial frontal cortex and cerebellum that was unique to the fear or anticipation of painful stimuli. Since previous studies have suggested that catastrophizing influences pain perception through increased attention to painful stimuli and enhanced affective and evaluative responses to pain, catastrophizing may be associated with heightened or unique activation in brain regions that modulate attention and emotional reactions to painful stimulation.

Functional imaging techniques have identified a number of brain regions that are activated with painful stimulation (Casey *et al*., 1996, 2001; Peyron *et al*., 2000). Pain stimulation is typically associated with activation in the secondary somatosensory cortex (SII), insular regions and the anterior cingulate cortex (ACC). Activation in the contralateral thalamus and primary somatosensory cortex (SI) is also observed, but less consistently. Activation of the lateral thalamus, SI, SII and insula appears to be related to the sensory discriminative aspects of pain, while the ACC may be related to the affective and attentional components of pain.

In the present study, we hypothesized that pain catastrophizing would be associated with greater activation in areas associated with the attentional and affective aspects of pain among chronic pain patients undergoing painful stimulation. We hypothesized that catastrophizing would be associated with activation in the ACC, insula, medial frontal cortex and cerebellum. As catastrophizing is often highly related to depression, and there is debate as to whether catastrophizing is a symptom of depression or a separate construct, associations between catastrophizing and brain activity were examined while statistically controlling for the influence of self-report of depressive symptoms.

Methods

Subjects

Twenty-nine patients, 19 female and 10 male, aged 18–60 years, who met the 1990 American College of Rheumatology criteria for fibromyalgia (Wolfe *et al*., 1990), were included. The study was approved by the Georgetown University Medical Center's institutional review board, and informed consent was obtained from all participants for study on the General Clinical Research Center. All patients underwent a comprehensive screening during which the diagnosis was confirmed and co-morbidities were evaluated. Exclusion criteria were severe physical impairment, medical conditions that were capable of causing patients' symptoms (e.g. morbid obesity, autoimmune/inflammatory diseases, cardiopulmonary disorders), uncontrolled endocrine or allergic disorders (i.e. hyper-/hypothyroidism, diabetes, allergic rhinitis), malignancy, severe psychiatric illnesses (e.g. schizophrenia, substance abuse), factors known to affect the hypothalamic–pituitary axis or autonomic function (e.g. cigarette smoking, daily intake of caffeine

exceeding the equivalent of two cups of coffee) or medication usage other than as-needed analgesics (excluding long-term narcotics).

Subjects who qualified for inclusion in the study were scheduled for a 2-day study protocol. They were asked to discontinue intake of antidepressants up to 4 weeks ahead of the appointment (depending on the drug), but were allowed to use non-steriodal anti-inflammatory drugs until 3 days before the appointment. On the first day of the study, patients completed the self-report questionnaires and were familiarized with the pain testing paradigm. On the following day, they participated in a pain psychophysical session and the functional MRI (fMRI) procedure.

Measures

Depression

The Center for Epidemiological Studies Depression Scale (Radloff, 1977) is a 20-item self-report questionnaire that assesses symptoms of depression in non-psychiatric adults. This instrument possesses strong psychometric properties and has demonstrated strong associations with other measures of depressive symptoms (Hertzog *et al*., 1990). The scale has acceptable validity among persons with physical disabilities (Berkman *et al*., 1986), and studies indicate that the measure has good predictive validity for identifying depression among persons with chronic pain (Turk *et al*., 1994; Geisser *et al*., 1997).

Catastrophizing

Catastrophizing was assessed using the catastrophizing subscale from the Coping Strategies Questionnaire (Rosenstiel and Keefe, 1983). The Coping Strategies Questionnaire assesses the frequency of patients' use of pain coping strategies. There are seven subscales consisting of six cognitive strategies (diverting attention, reinterpreting pain sensations, ignoring pain sensations, coping self-statements, praying or hoping, and catastrophizing) and one behavioural strategy (increasing activity level). Subjects use a 7-point scale to rate how often they use each strategy to cope with pain. Subjects are also asked to make two ratings of their appraisal of the overall effectiveness of coping strategies (how much control they have over pain and how much they are able to decrease pain). Reliability coefficients for each of the subscales range from 0.71 to 0.85 (Rosenstiel and Keefe, 1983).

Clinical pain

Clinical pain experience of subjects was assessed using the short-form of the McGill Pain Questionnaire (MPQ; Melzack, 1987). This questionnaire contains 15 pain adjectives. The author reports that the scale is sensitive to change produced by various pain interventions, and is highly correlated with the parent scale (Melzack, 1987).

Self-report of clinical pain intensity was also obtained by asking subjects to rate their pain during the past week on a visual analogue scale (VAS). The scale was 100 mm long and anchored by the statements 'no pain' on the left and 'the most intense pain imaginable' on the right. Separate VAS scales were used to measure subjects' level of pain on the day of testing, pain in the past month, pain intensity on bad days and pain intensity on good days. VAS ratings have demonstrated good reliability (Revill *et al*., 1976; Boeckstyns and Backer, 1989) and concurrent validity when compared with other methods of pain measurement (Downie *et al*., 1978; Jensen *et al*., 1989).

Experimental pain assessment

During the pain testing session, pressure pain sensitivity was evaluated by subjective scaling of multiple pressure pain sensations of suprathreshold intensities. Discrete 5 s pressure stimuli were applied to the fixated left thumbnail with a 1 cm^2 hard rubber probe. Previous studies have shown that 'neutral' regions, such as the thumb, accurately reflect an individual's overall pressure pain sensitivity (Petzke *et al*., 2003). The rubber probe was attached to a hydraulic piston, which was connected via a combination of valves to a second piston. Application of calibrated weights to the second piston produced controlled, repeatable pressure pain stimuli of rectangular waveform. Subjects rated the intensity of pressure pain sensations using a combined numerical analogue descriptor scale, developed from previously quantified verbal descriptors (Gracely *et al*., 1979). The session began with a series of stimuli presented in a predictable, 'ascending' fashion, beginning at 0.5 kg/cm^2 and increasing in 0.5 kg/cm^2 intervals up to tolerance or to a maximum of 10 kg/cm^2. Following the ascending series, 36 stimuli were delivered at 20 s intervals in random order, using the multiple random staircase method (Gracely *et al*., 1988). The multiple random staricase method is response-dependent, i.e. it determines the stimulus intensity needed to elicit a specified response. In this study, we determined the stimulus intensities sufficient to elicit pain threshold, mild pain (7.5 out of 21 scale units) and slightly intense pain (13.5 out of 21 scale units).

Functional imaging

MRI and fMRI scans were performed on a 1.5 T vision system (Siemens, Munich, Germany). A T1-weighted MRI anatomical scan session [echo time (TE) 4 ms; recovery time (TR) 9.7 ms; flip angle 12°; 256 × 256 pixel matrix; field of vision (FOV) 256 mm; 1 mm^3 voxels, acquired non-interleaved in the sagittal direction] was followed by two functional scan sessions using multi-slice, echo-planar imaging fMRI acquisition (TE 40 ms; TR 5 s; repetition time 5 s; flip angle 90°; 64 × 64 pixel matrix; FOV 192 mm; 50 horizontal 3 mm slices). These parameters allowed coverage of the entire brain with 3 mm^3 voxels within 5 s.

During each fMRI session, the first three scans were discarded to allow for saturation of the tissue. Starting on the fourth scan, pressure stimuli of 25 s duration ('on' condition) were alternated with 25 s resting periods ('off' condition). Onset and offset of a stimulus was coincident with the beginning of a scan, allowing the acquisition of five scans during each of 12 'on' and 12 'off' conditions.

During the 'on' condition, different stimulus intensities were presented in random sequence. These stimulus intensities included three stimuli chosen on the basis of the baseline pain testing, sufficient to elicit a rating of 13.5 out of 20 (slightly intense pain). The analysis was performed on the scans acquired during the slightly intense pain conditions and the 'off' conditions.

Imaging analysis

Imaging data were analysed with MEDx (Sensor Systems, Sterling, VA). The functional images were corrected for head motion and intensity differences. Head motion was determined by motion detection software and visual inspection of raw and processed images. Head motion greater than a half a voxel was deemed *a priori* to be unacceptable, and images meeting this criterion were to be excluded. None of the scans had head motion exceeding this

criterion, so all images were included in the analyses. Acceptable motion-corrected images were spatially smoothed at 6 mm full width at half maximum.

The brain volumes collected during 'on' conditions were compared with the brain volumes collected during 'off' conditions by *t* test. Resultant *Z* statistical volumes and mean differences volumes were registered into standardized space using the statistical parametric mapping (SPM96) echo-planar imaging template and re-sliced to 2 mm^3 voxels.

Anatomic regions were identified (i) by inspection of individual functional images superimposed on an individual structural image; and (ii) by conversion of the coordinates to the coordinate system of the Talairach–Tournoux atlas and localization using this atlas (Talairach and Tournoux, 1988) and automated software (Lancaster *et al*., 2000).

Results

The first step in the data analyses involved examining the relationship between Coping Strategies Questionnaire catastrophizing scores and scores on the Center for Epidemiological Studies Depression Scale. The correlation was marginally significant ($r = 0.36$, $P = 0.06$). To statistically control for self-reported depression in catastrophizing scores, standardized residuals were calculated by regressing Center for Epidemiological Studies Depression Scale scores on the catastrophizing scores of the Coping Strategies Questionnaire. The remaining analyses examining the relationship between catastrophizing and brain activity used these standardized residuals.

The relationship between pain catastrophizing and brain activity was examined in two ways. First, correlation coefficients were computed between the standardized residual catastrophizing scores, demographic information, clinical and experimental pain, and brain activity. Pearson correlations were examined between continuous data elements, while a Spearman ρ correlation was computed to examine the relationship between residual catastrophizing scores and gender.

To determine if the findings of the correlational analysis could be replicated utilizing a different methodological approach, a second analysis was performed classifying subjects as high and low catastrophizers based on a median split of the residual catastrophizing scores. The median residual catastrophizing score in the sample was –0.15 (range –2.41 to 4.6). Fifteen subjects who had a residual score of –0.15 or less were classified as low catastrophizers, while 14 subjects with a higher score were designated as high catastrophizers. Group differences were examined using *t* tests for continuous dependent variables, and a χ^2 analysis was performed to examine group differences in terms of gender.

Correlational analyses

The associations between catastrophizing and pain and demographic variables are presented in Table 1. Catastrophizing was not significantly associated with age and gender nor with experimental forms of pressure pain (i.e. pain threshold, mild or slightly intense). Residual catastrophizing scores were significantly related to clinical pain, as higher scores were significantly associated with higher affective and total pain ratings on the MPQ short form ($r = 0.63$, $P < 0.001$ and $r = 0.41$, $P = 0.03$, respectively), but were not significantly associated with sensory ratings. Residual catastrophizing scores were significantly associated with VAS ratings of pain during the past month ($r = 0.37$, $P = 0.05$), and on bad days ($r = 0.50$, $P < 0.01$). No significant associations were observed between catastrophizing and either ratings of pain on the day of testing or level of pain on good days.

Table 1 *Correlations between catastrophizing and demographic and pain variables*

Variable	Pearson correlation coefficient
Age	–0.34
Sex	0.03
MPQ sensory	0.30
MPQ affective	0.63***
MPQ total	0.41*
VAS today	0.28
VAS past month	0.37*
VAS pain on bad days	0.50**
VAS pain on good days	0.16
Pressure pain threshold (low; kg/cm^2)	–0.03
Pressure pain moderate (medium; kg/cm^2)	–0.23
Pressure pain slightly intense (high; kg/cm^2)	–0.01

***$P < 0.001$; **$P < 0.01$; *$P < 0.05$.

Despite catastrophizing being unrelated to reports of evoked pain, it was associated with brain activity during slightly intense pain stimulation (Table 2). Activation is expressed as the *Z* change score comparing activity during slightly intense pain stimulation with the baseline condition. Higher catastrophizing scores were significantly associated with greater activation in the ipsilateral claustrum ($r = 0.51$, $P < 0.01$), ipsilateral medial frontal gyrus ($r = 0.47$, $P < 0.01$), ipsilateral cerebellum ($r = 0.43$, $P < 0.01$), ipsilateral postcentral gyrus (SII; $r = 0.41$, $P < 0.01$) and the ipsilateral middle frontal gyrus ($r = 0.41$, $P < 0.01$). Catastrophizing was both significantly and positively associated with activation in the contralateral hemisphere in the anterior ACC ($r = 0.43$, $P < 0.01$), medial/posterior ACC ($r = 0.41$, $P < 0.01$), medial frontal gyrus ($r = 0.40$, $P < 0.01$) and lentiform ($r = 0.40$, $P < 0.01$).

Group analyses

Examining the demographic and pain variables, the groups of high and low catastrophizers did not differ significantly in terms of age or gender, nor did they differ significantly in their perception of experimental pressure pain. The groups did differ significantly on the measures of clinical pain, as

Table 2 *Significant correlations between catastrophizing and brain activation during painful stimulation controlled for depression*

Brain region	Coordinates			Pearson *r*
	x	*y*	*z*	
Ipsilateral claustrum	–30	6	5	0.51*
Ipsilateral middle frontal gyrus (BA 6)	–46	3	51	0.47*
Ipsilateral cerebellum	–30	–68	–37	0.43*
Contralateral ACC (BA 32)	8	15	36	0.43*
Ipsilateral postcentral gyrus (SII)	–63	–21	14	0.41*
Ipsilateral middle frontal gyrus (BA 11)	–30	44	–12	0.41*
Contralateral ACC (BA 24)	2	11	27	0.41*
Contralateral medial frontal gyrus (BA 6)	2	–17	56	0.40*
Contralateral lentiform	14	6	3	0.40*

*$P < 0.01$.

Table 3 *Mean (SD) of high and low catastrophizing groups on age and pain measures*

Variable	Group		*t* value
	Low	High	
Age (years)	44.6 (8.8)	38.9 (10.6)	1.57
MPQ sensory	6.5 (5.0)	12.8 (6.3)	3.0*
MPQ affective	1.8 (1.6)	3.9 (2.0)	3.1*
MPQ total	8.1 (6.2)	16.7 (7.5)	3.4*
VAS today (mm)	39.3 (29.3)	65.0 (14.9)	2.9*
VAS past month (mm)	45.3 (20.8)	67.9 (7.5)	3.8*
VAS pain on bad days (mm)	69.0 (17.9)	87.5 (8.9)	3.5*
VAS pain on good days (mm)	18.3 (14.4)	37.5 (15.9)	3.4*
Pressure pain threshold (kg/cm^2)	1.0 (0.7)	0.9 (0.6)	0.6
Pressure pain moderate (kg/cm^2)	3.0 (1.4)	2.0 (1.0)	2.0
Pressure pain slightly intense (kg/cm^2)	4.6 (1.7)	4.2 (2.2)	0.6

*$P < 0.01$.

high catastrophizers had significantly higher scores on the sensory ($t = 3.0$, $P < 0.01$), affective ($t = 3.1$, $P < 0.01$) and total ($t = 3.4$, $P < 0.01$) pain rating indexes of the MPQ short form. High catastrophizers also rated their clinical pain higher on the day of testing ($t = 2.9$, $P < 0.01$), during the past month ($t = 3.8$, $P < 0.01$), on bad days ($t = 3.5$, $P < 0.01$) and on good days ($t = 3.4$, $P < 0.01$).

Regions with increased fMRI signal in response to slightly intense painful pressure are presented in Table 4 for high and low catastrophizers. Corrected for multiple comparisons, a *Z* score of 3.5 corresponded to a *P* value of 0.05. *Z* scores of $\geqslant 3.5$ were determined as significant activation in a region. Both groups displayed significant increases in fMRI signal in contralateral insula, SI, SII, inferior parietal lobule (IPL) and thalamus, and in ipsilateral SI, SII anterior cerebellum, posterior cerebellum, posterior cingulate gyrus, superior frontal gyrus and inferior frontal gyrus. Note that the activation in ipsilateral SII was twice as large among high catastrophizers.

In addition to activations common to both groups, activations in several regions were observed only in the high catastrophizing group. These data are presented in Table 5. High catastrophizers displayed activation in the contralateral anterior ACC, and in both the contralateral and ipsilateral lentiform. There were no such unique activations in the low catastrophizing group.

Table 6 shows the results of a *t* test of the mean differences in fMRI signal in response to slightly intense painful pressure between both groups. Patients scoring high in catastrophizing displayed six regions with a significantly higher increase in fMRI signal: ipsilateral SII, ACC, superior frontal gyrus, medial frontal gyrus, premotor cortex and contralateral IPL. Three of these areas (ipsilateral SII, middle and medial frontal gyrus) corresponded to areas associated with the level of catastrophizing. Two of these areas (ipsilateral SII and contralateral IPL) corresponded to areas that showed significantly increased fMRI signal in response to slightly intense pain in both groups (Table 4). On the other hand, patients scoring low in catastrophizing displayed a significantly higher increase in fMRI signal only in ipsilateral IPL.

Discussion

The results support our hypothesis that pain catastrophizing, independent of self-report of depressive symptoms, is associated with the magnitude of neural activation evoked by

Table 4 *Brain areas commonly activated in high and low catastrophizing groups*

Brain region	Coordinates			*Z* score
	x	*y*	*z*	
Ipsilateral SII (BA 40)				
High	–69	–20	18	7.31
Low	–61	–20	21	3.58
Ipsilateral SI (BA 2)				
High	–63	–25	36	4.99
Low	–69	–24	34	5.82
Ipsilateral cerebellum anterior lobe				
High	–36	–54	–26	5.96
Low	–32	–54	–26	5.14
Ipsilateral cerebellum posterior lobe				
High	–36	–69	–23	5.25
Low	–30	–65	–20	5.31
Ipsilateral posterior cingulate gyrus				
High	–4	–22	27	4.04
Low	–4	–20	34	3.61
Ipsilateral superior frontal gyrus (BA 6)				
High	–6	24	58	4.25
Low	–16	12	51	3.22
Ipsilateral inferior frontal gyrus				
High	–53	8	14	4.63
Low	–63	13	23	3.94
Contralateral insula (BA 13)				
High	46	2	5	5.24
Low	38	4	9	5.24
Contralateral SII (BA 40)				
High	61	–20	19	6.16
Low	65	–24	21	4.80
Contralateral inferior parietal lobule (BA 40)				
High	51	–32	55	4.00
Low	53	–40	52	3.51
Contralateral SI (BA 2)				
High	61	–17	43	5.02
Low	55	–16	38	4.97
Contralateral thalamus				
High	8	–11	4	3.36
Low	4	–11	8	4.48

painful stimulation. Correlational analyses showed an association between catastrophizing and pain-evoked activation in the bilateral dorsolateral prefrontal cortex, ipsilateral claustrum, cerebellum and parietal cortex, and contralateral rostral anterior cingulate gyrus, medial frontal cortex and lentiform. Group analyses based on a median split of residual pain catastrophizing scores indicated that persons both high and low on catastrophizing displayed a similar pattern of activations in the contralateral SI, SII, insula, thalamus and IPL, and the ipsilateral SI, SII, cerebellum, rostral ACC and dorsolateral prefrontal cortex. This pattern is consistent with the cerebral response to pressure pain reported recently using similar stimulus parameters (Gracely *et al*., 2002). Neuronal activation in ipsilateral SII, however, was more than twice as large in subjects high on catastrophizing compared with subjects low in catastrophizing. In addition, high catastrophizers displayed unique activation in the contralateral rostral ACC, and ipsilateral and contralateral lentiform. Figure 1 shows that the location of the unique activation of the contralateral ACC in the group analysis was very close to the region that was associated with catastrophizing in the correlational analysis.

As hypothesized, catastrophizing demonstrated significant relationships with activation in brain structures that have been found to be associated not only with pain processing, but also with the attentional and emotional aspects of pain. In addition, catastrophizing was associated with activation in the premotor cortex and in the lentiform nuclei. This latter activation is consistent with previous research suggesting that catastrophizing is associated with greater pain behaviour and increased emotional expression in response to pain (Sullivan *et al*., 2001). Consistent with the studies mentioned earlier, catastrophizing was associated with greater activation in the cerebellum and medial frontal gyrus. These regions were among those identified as uniquely activated during anticipation of pain (Ploghaus, 1999), although, in the present study, activity in the insula was not uniquely associated with catastrophizing. In addition, activation was observed in areas

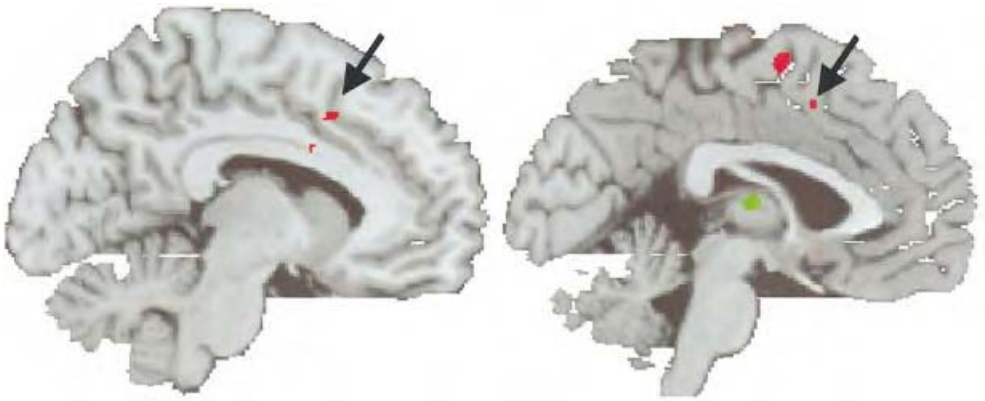


Fig. 1 Examples from association and group analyses. Significant influence of catastrophizing on activity in the contralateral rostral ACC (BA 32) is shown in red for the association analysis (left, Table 2) and for the group scoring high in catastrophizing (right, Table 5). The green region in the right figure shows common activation in the thalamus in both high and low catastrophizing groups (Table 4).

Table 5 *Brain areas uniquely activated in the high catastrophizing group*

Brain region	Coordinates			*Z* score
	x	*y*	*z*	
Contralateral ACC (BA 32)	4	12	40	4.02
Ipsilateral lentiform	–14	4	5	4.36
ContralateraI lentiform	22	6	3	3.76

uniquely associated with catastrophizing in the SII and the rostral ACC. The dorsal, rostral ACC may be preferentially involved in cognition functions (e.g. selective attention), while the ventral, perigenual portion may be more involved in emotional processing (Davidson *et al*., 2002). Expectation of pain has been associated with increased activity in SII (Sawamoto *et al*., 2000), and the anterior ACC is activated during attention-demanding tasks (Davis *et al*., 2000). Activation of these stuctures further suggests that catastrophizing may influence pain perception through its influence on attention.

Although catastrophizing was significantly associated with clinical pain, it was not associated with differences in experimental pain perception. This suggests that the fMRI findings are not due to differences in the intensity of the simulation used during scanning. While one might predict that catastrophizing might be associated with heightened perception of experimental pain, as shown in previous studies in normals and clinical populations (Geisser *et al*., 1992, 2003), we believe that the lack of a relationship between catastrophizing and experimental pain is due to the experimental pain methods used to determine the stimulus intensities. Petzke *et al*. (2003) propose that experimental methods that employ gradually ascending methods of stimulation are more likely to be subject to biases produced by psychological factors. The authors compared four different methods of experimental pain stimulation methods, and contrasted gradually ascending methods with those employing the random staircase method utilized in the present study. The authors found that experimental pain measures that employed gradually ascending methods of stimulation were significantly correlated with measures of psychological distress, while assessment of experimental pain utilizing the random staircase method was not. However, all the measures were significantly associated with clinical pain. These findings suggest that perceived pain intensity as determined by the random staircase method is less likely to be influenced by psychological factors such as catastrophizing, and suggest that this measure is more reflective of the sensory aspect of pain and less susceptible to the influence of factors reflecting the affective and evaluative components of pain. This is consistent with the finding that catastrophizing in the present study was associated primarily with structures involved in the affective and evaluative aspects of pain processing, as discussed further below. While unique patterns of activation associated with catastrophizing are evident during stimulation, the methodology used to determine pain ratings in the present study minimized the influence of the catastrophizing on the determination of these values.

In addition, the influence of catastrophizing on pain perception may be modulated by the perceived threat value of the stimulus. For example, studies examining perceptual differences among patient groups that use paradigms that do not involve the administration of noxious stimuli (e.g. Peters *et al*., 2000) have not observed a relationship between catastrophizing and perception. Thus, it is also possible that the threat value of the stimuli utilized in the present study was low, attenuating a relationship between catastrophizing and the perception of experimental pain.

The regions found to be associated with catastrophizing in this study include not only structures involved in emotional or attentional processing of painful stimuli, but also sensory structures that are likely to be involved in encoding the magnitude of evoked pain sensations. Activity in SI and SII has been shown to be associated with the magnitude of pain evoked by contact heat (Coghill *et al*., 1999) and, in our own laboratory, we have found that the magnitude of painful

Table 6 *Brain regions showing significantly higher activations in one of the groups*

Group	Brain region	Coordinates			*Z* score
		x	*y*	z	
High	Ipsilateral SII	–69	–22	18	3.45*,+
	Ipsilateral ACC (BA 32)	–14	15	36	3.33
	Ipsilateral superior frontal gyrus (BA 11)	–20	59	–21	3.24
	Ipsilateral medial frontal gyrus (BA 6)	–48	–1	52	3.52*
	Contralateral medial frontal gyrus (BA 6)	2	–13	52	4.00*
	Contralateral IPL (BA 40)	53	–26	31	3.58+
Low	Ipsilateral IPL (BA 40)	–48	–46	58	3.79

*Corresponds to Table 2; +corresponds to Table 4.

pressure is associated with activity in SI and SII (Grant *et al*., 2001). The association found between brain activity and catastrophizing, however, was not limited to somatosensory regions but also included the ACC. Both the ACC and SII may be involved in evaluative or affective processing, suggesting that catastrophizing is associated with the affective and evaluative aspects of pain. Thus, activation in SII associated with catastrophizing in the present study probably reflects an assocation between catastrophizing and affective and evaluative pain processing, as catastrophizing was not related to activation in SI. This is supported in the present study through the unique patterns of activation observed and by the fact that catastrophizing was more highly associated with the affective and total subscales of the MPQ short form, replicating findings from a previous study (Geisser *et al*., 1994).

It should be noted that the study design was cross-sectional, and therefore no conclusions can be made regarding cause–effect relationships. Although it is possible that pain catastrophizing may occur in response to pain, in the present study, catastrophizing was assessed prior to fMRI evaluation, suggesting that catastrophizing was not a reaction to experimental pain stimulation. In addition, it is possible that findings may be related to the influence of other variables associated with catastrophizing, such as clinical pain. In the group analyses, the high and low catastrophizing groups differed significantly on ratings of clinical pain on the day of testing. However, these differences in clinical pain ratings may be due to the influence of catastrophizing, as many clinical pain measures are impacted by affective and evaluative responses to pain. For example, Clark *et al*. (2002) found that a unidimensional pain rating scale, similar to the one used in the present study, was significantly associated with categories of affective pain desciptors, but not significantly associated with sensory pain descriptors.

While we observed group differences in clinical pain on the day of testing, catastrophizing was not significantly correlated with this variable. This suggests that it is unlikely that the findings of the correlational analyses are spuriously due to the influence of clinical pain. In addition, while catastrophizing was associated with activation in some structures that are uniquely associated with clinical pain states, no relationship was observed between catastrophizing and other structures known be differentially activated in clinical pain populations, such as SI. For example, Flor *et al*. (1995), found that activation in primary somatosensory cortex correlated very highly ($r = 0.93$) with clinical pain among persons with phantom limb pain. Thus, we believe the pattern of findings observed in the group analysis are probably not due to differences in clinical pain intensity.

Given that catastrophizing and clinical pain tend to covary, it would be beneficial for future studies to examine whether interventions that selectively influence catastrophizing or clinical pain uniquely alter cerebral patterns of pain activation. However, since these variables may be intrinsically linked, it may be difficult to find interventions that selectively influence clinical pain without altering catastrophizing, or vice versa. Alternatively, it might be beneficial to study the relationship between catastrophizing and pain activation in normal, healthy populations, as catastrophizing has also been found to influence pain perception in these populations (Geisser *et al*., 1992).

In summary, catastrophizing appears to be uniquely associated with activation in brain areas involved in attention to pain, emotion and motor activity. The findings support the hypothesis that catastrophizing influences pain perception through its influence on affective and attentional responses to pain. It would be beneficial to examine whether brain responses to pain among persons who are high in catastrophizing can be altered through manipulations designed to change the threat value of the stimulus, or attention to the stimulus. The findings also suggest that interventions designed to alter attention to or the perceived threat of clinical pain may be beneficial among persons with pain who catastrophize about their condition.

Acknowledgement

This research was supported by The Department of Defence (Army) Grant DAMD 17-00-2-0018.

References

Berkman LF, Berkman CS, Kasl S, Freeman DH Jr, Leo L, Ostfeld AM, et al. Depressive symptoms in relation to physical health and functioning in the elderly. Am J Epidemiol 1986; 124: 372–88.

Bigos SJ, Battie MC, Spengler DM, Fisher LD, Fordyce WE, Hansson T,

et al. A longitudinal, prospective study of industrial back injury reporting. Clin Orthop 1992; (279): 21–34.

Boeckstyns MEH, Backer M. Reliability and validity of the evaluation of pain in patients with total knee replacement. Pain 1989; 38: 29–33.

Brooks JC, Nurmikko TJ, Bimson WE, Singh KD, Roberts N. fMRI of thermal pain: effects of stimulus laterality and attention. Neuroimage 2002; 15: 293–301.

Burton AK, Tillotson MK, Main CJ, Hollis S. Psychosocial predictors of outcome in acute and sub-chronic low back trouble. Spine 1995; 20: 722–8.

Casey KL, Minoshima S, Morrow TJ, Koeppe RA. Comparison of human cerebral activation pattern during cutaneous warmth, heat pain, and deep cold pain. J Neurophysiol 1996; 76: 571–81.

Casey KL, Morrow TJ, Lorenz J, Minoshima S. Temporal and spatial dynamics of human forebrain activity during heat pain: analysis by positron emission tomography. J Neurophysiol 2001; 85: 951–9.

Clark WC, Yang JC, Tsui SL, Ng KF, Clark SB. Unidimensional pain rating scales: a multidimensional affect and pain survey (MAPS) analysis of what they really measure. Pain 2002; 98: 241–7.

Coghill CR, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. J Neurophysiol 1999; 82: 1934–43.

Crombez G, Eccleston C, Baeyens F, Eelen P. When somatic information threatens, catastrophic thinking enhances attentional interference. Pain 1998; 75: 187–98.

Crombez G, Eccleston C, Van den Broeck A, Van Houdenhove B, Goubert L. The effects of catastrophic thinking about pain upon attentional interference by pain: no mediation of negative affectivity in healthy volunteers and in low back pain patients. Pain Res Manag 2002; 7: 31–44.

Davidson RJ, Pizzagalli D, Nitschke JB, Putman K. Depression: perspectives from affective neuroscience. Annu Rev Psychol 2002; 53: 545–74.

Davis KD, Hutchison WD, Lozano AM, Tasker RR, Dostrovsky JO. Human anterior cingulate cortex neurons modulated by attention-demanding tasks. J Neurophysiol 2000; 83: 3575–7.

Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. Ann Rheum Dis 1978; 37: 378–81.

Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, et al. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 1995; 375: 482–4.

Gatchel RJ, Polatin PB, Mayer TG. The dominant role of psychosocial risk factors in the development of chronic low back pain disability. Spine 1995; 20: 2702–9.

Geisser ME, Roth RS. Knowledge of and agreement with pain diagnosis: relation to pain beliefs, pain severity, disability, and psychological distress. J Occup Rehabil 1998; 8: 73–88.

Geisser ME, Robinson ME, Pickren W. Coping styles among pain sensitive and pain tolerant individuals on the cold-pressor test. Behav Ther 1992; 23: 31–41.

Geisser ME, Robinson ME, Keefe FJ, Weiner ML. Catastrophizing, depression and the sensory, affective and evaluative aspects of chronic pain. Pain 1994; 59: 79–83.

Geisser ME, Roth RS, Robinson ME. Assessing depression among persons with chronic pain using the Center for Epidemiological Studies-Depression Scale and the Beck Depression Inventory: a comparative analysis. Clin J Pain 1997; 13: 163–70.

Geisser ME, Casey KL, Brucksch CB, Ribbens CM, Appleton BB, Crofford LJ. Perception of noxious and innocuous heat stimulation among healthy women and women with fibromyalgia: association with mood, somatic focus, and catastrophizing. Pain 2003; 102: 243–50.

Gracely RH, Dubner R, McGrath PA. Narcotic analgesia: fentanyl reduces the intensity but not the unpleasantness of painful tooth pulp sensations. Science 1979; 203: 1261–3.

Gracely RH, Lota L, Walter DJ, Dubner R. A multiple random staircase method of psychophysical pain assessment. Pain 1988; 32: 55–63.

Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002; 46: 1333–43.

Grant MAB, Farrell MJ, Kumar R, Clauw DJ, Gracely, RH. fMRI evaluation of pain intensity coding in fibromyalgia patients and controls. Arthritis Rheum 2001; 44: 394.

Hertzog C, Van Alstine J, Usala PD, Hultsch D, Dixon R. Measurement properties of the center for epidemiological studies depression scale (CES-D) in older populations. Psychol Assess 1990; 2: 64–72.

Jensen MP, Karoly P, O'Riordan EF, Bland F Jr, Burns RS. The subjective experience of acute pain: an assessment of the utility of 10 indices. Clin J Pain 1989; 5: 153–9.

Jensen MP, Ehde DM, Hoffman AJ, Patterson DR, Czerniecki JM, Robinson LR. Cognitions, coping and social environment predict adjustment to phantom limb pain. Pain 2002; 95: 133–42.

Keefe FJ, Brown GK, Wallston KA, Caldwell DS. Coping with rheumatoid arthritis pain: catastrophizing as a maladaptive strategy. Pain 1989; 37: 51–56.

Keefe FJ, Caldwell DS, Williams DA, Gil KM, Mitchell D, Robertson C, et al. Pain coping skills training in the management of osteoarthritic knee pain—II: follow-up results. Behav Ther 1990; 21: 435–47.

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas ES, Rainey L, et al. Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp 2000; 10: 120–31.

Melzack R. The short-form McGill Pain Questionnaire. Pain 1987; 30: 191–7.

Melzack R, Wall PD. The challenge of pain. New York: Basic Books; 1982.

Nachemson AL. Advances in low-back pain. Clin Orthop 1985; 200: 266–78.

Peters ML, Vlaeyen JWS, van Drunen C. Do fibromyalgia patients display hypervigilance for innocuous somatosensory stimuli? Application of a body scanning reaction time paradigm. Pain 2000; 86: 283–92.

Petzke F, Gracely RH, Park KM, Ambrose K, Clauw DJ. What do tender points measure? Influence of distress on 4 measures of tenderness. J Rheumatol 2003; 30: 567–74.

Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis 2000. Neurophysiol Clin 2000; 30: 263–88.

Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, et al. Dissociating pain from its anticipation in the human brain. Science 1999; 284: 1979–81.

Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977; 1: 385–401.

Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. Anaesthesia 1976; 31: 1191–8.

Rosenstiel AK, Keefe FJ. The use of coping strategies in chronic low back pain patients: relationship to patient characteristics and current adjustment. Pain 1983; 17: 33–44.

Sawamoto N, Honda M, Okada T, Hanakawa T, Kanda M, Fukuyama H, et al. Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: an event-related functional magnetic resonance imaging study. J Neurosci 2000; 20: 7438–45.

Sullivan MJL, D'Eon JL. Relation between catastrophizing and depression in chronic pain patients. J Abnorm Psychol 1990; 99: 260–3.

Sullivan MJL, Standish W, Waite H, Sullivan M, Tripp DA. Catastrophizing, pain and disability in patients with soft-tissue injuries. Pain 1998; 77: 253–60.

Sullivan MJL, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, et al. Theoretical perspectives on the relation between catastrophizing and pain. Clin J Pain 2001; 17: 52–64.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.

Turk DC, Okifuji A. Detecting depression in chronic pain patients: adequacy of self-reports. Behav Res Ther 1994; 32: 9–16.

Wolfe FW, Smythe HA, Yunas MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Arthritis Rheum 1990; 33: 160–72.

Neurobiology of Disease

Decreased Central μ-Opioid Receptor Availability in Fibromyalgia

Richard E. Harris,[1] Daniel J. Clauw,[1] David J. Scott,[2] Samuel A. McLean,[3] Richard H. Gracely,[1] and Jon-Kar Zubieta[2,4]

[1]Department of Internal Medicine, [2]Department of Psychiatry and Molecular and Behavioral Neuroscience Institute, and Departments of [3]Emergency Medicine and [4]Radiology, The University of Michigan, Ann Arbor, Michigan 48109

The underlying neurophysiology of acute pain is fairly well characterized, whereas the central mechanisms operative in chronic pain states are less well understood. Fibromyalgia (FM), a common chronic pain condition characterized by widespread pain, is thought to originate largely from altered central neurotransmission. We compare a sample of 17 FM patients and 17 age- and sex-matched healthy controls, using μ-opioid receptor (MOR) positron emission tomography. We demonstrate that FM patients display reduced MOR binding potential (BP) within several regions known to play a role in pain modulation, including the nucleus accumbens, the amygdala, and the dorsal cingulate. MOR BP in the accumbens of FM patients was negatively correlated with affective pain ratings. Moreover, MOR BP throughout the cingulate and the striatum was also negatively correlated with the relative amount of affective pain (McGill, affective score/sensory score) within these patients. These findings indicate altered endogenous opioid analgesic activity in FM and suggest a possible reason for why exogenous opiates appear to have reduced efficacy in this population.

Key words: **fibromyalgia; opioid; pain; chronic; positron emission tomography; μ**

Introduction

Sensory perceptions can serve to alert organisms of present and/or future danger. This is particularly evident for the sensation of acute pain. However, neural pain pathways that originally function to warn of potential harm may also become dysfunctional and lead to maladaptive diseased states of a chronic nature (Woolf, 2004). Fibromyalgia (FM), a condition of idiopathic chronic pain, may be one such disorder.

FM is defined on the basis of tenderness and spontaneous chronic widespread pain (Wolfe et al., 1990) and afflicts 2–4% of individuals in industrialized countries (Wolfe et al., 1995). In addition many FM patients also suffer from psychiatric illnesses such as depression (Giesecke et al., 2003). Unfortunately, because of the lack of readily identifiable peripheral pathology in FM (e.g., muscle or joint inflammation), acceptance of this condition by medical practitioners has been slow (Cohen, 1999).

A growing body of scientific literature suggests that the lack of apparent peripheral pathology in FM might be explained by a primary disturbance in central rather than peripheral pain processing (Clauw and Chrousos, 1997). Data from psychophysical pain testing (Petzke et al., 2003), quantitative EEG (Lorenz et al., 1996), and functional neuroimaging (Gracely et al., 2002; Cook et al., 2004) supports this theory. FM patients display increased neural activations in pain regions such as the insula, the somatosensory cortex, and the cingulate, in response to pressure pain. These same areas are activated in healthy control participants, albeit at higher objective stimulus intensities. Although this suggests that altered pain processing of experimental stimuli occurs in FM, the underlying neurobiology driving clinical symptoms such as pain and depression is unknown.

One potential reason for pain symptoms in FM may be inadequate descending antinociceptive activity. Research suggests that such activity may be deficient or absent in FM (Julien et al., 2005). In humans, the two principal descending inhibitory pain pathways involve either norepinephrine/serotonin or opioids, but psychophysical studies are incapable of distinguishing which of these pathways may be affected. FM patients display low CSF levels of biogenic amines, suggesting a possible deficiency of descending serotonergic/noradrenergic pathways in this condition (Russell et al., 1992). CSF levels of endogenous enkephalins, however, have been noted to be high, which suggests an excess of endogenous opioids in FM (Baraniuk et al., 2004). Although no trials of exogenous opioids in FM have been performed, opioids are not anecdotally found to be useful in treating this and related conditions (Rao and Clauw, 2004). Thus, existing data support a deficit in descending analgesic activity in the serotonergic/noradrenergic system and an overactive opioidergic system; however, as of yet, there is no direct evidence of this.

We used positron emission tomography (PET) to further investigate opioid antinociceptive activity in FM. [^{11}C]carfentanil, a selective μ-opioid receptor (MOR) radiotracer, was used to

Received May 7, 2007; revised Aug. 1, 2007; accepted Aug. 2, 2007.

This work was supported by Department of Army Grant DAMD-17/002-0018, Grant M01-RR000042 from the National Center for Research Resources, a component of the National Institutes of Health (NIH), and NIH Grant R01 AT 001415 (J.-K.Z.). R.E.H. was supported by NIH–National Center for Complementary and Alternative Medicine Grant K01 AT01111-01. S.A.M. was supported by NIH Grant K12 RR017607-01. There are no conflicts of interest for any of us with the material presented. We acknowledge V. Napadow and S. Harte for their careful review of this manuscript.

Correspondence should be addressed to Dr. Richard E. Harris, Chronic Pain and Fatigue Research Center, 24 Frank Lloyd Wright Drive, P.O. Box 385, Lobby M, Ann Arbor, MI 48106. E-mail: reharris@med.umich.edu.

DOI:10.1523/JNEUROSCI.2849-07.2007

 0270-6474/07/2710000-07$15.00/0

assess baseline receptor availability *in vivo* [binding potential (BP)] in patients and pain-free control participants. We hypothesized that patients with FM may have decreased MOR receptor availability, because they have increased levels of endogenous opioids in the CSF (Baraniuk et al., 2004), possibly leading to receptor downregulation. In addition, we investigated the association of MOR availability with both the affective and sensory dimensions of clinical pain. Finally, as an exploratory analysis, we examined the relationship between MOR availability and depression within FM patients.

Materials and Methods

Participants

As part of an ongoing study investigating the impact of acupuncture treatment in FM, 17 female right-handed patients (age, 44.8 ± 13.7 years; duration of FM diagnosis, 8.4 ± 6.0 years) were examined with PET. Seventeen right-handed age- and sex-matched control participants (age, 40.4 ± 11.2 years) were used as a comparison with the FM group. All analyses were performed on data acquired before acupuncture treatment. Participants gave written informed consent, and the study protocol was approved by the local Institutional Review Board and the Radioactive Drug Research Committee.

All patients (1) met the American College of Rheumatology 1990 criteria (Wolfe et al., 1990) for the diagnosis of FM for at least 1 year; (2) had continued presence of pain >50% of days; (3) were willing to limit the introduction of any new medications or treatment modalities for control of FM symptoms during the study; (4) were >18 and <75 years of age; (5) were female; (6) were right handed; (7) had no alcohol intake 48 h before PET studies; and (8) were capable of giving written informed consent. Patients were excluded if they (1) had used narcotic analgesics within the past year or had a history of substance abuse; (2) had presence of a known coagulation abnormality, thrombocytopenia, or bleeding diathesis; (3) had the presence of concurrent autoimmune or inflammatory disease, such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, etc., that causes pain; (4) had concurrent participation in other therapeutic trials; (5) were pregnant or nursing mothers; (6) had severe psychiatric illnesses (current schizophrenia, major depression with suicidal ideation, or substance abuse within 2 years); (7) had current major depression; or (8) had contraindications to PET. No patients were taking or had a previous history of opioid medication use. Ten of the FM participants were taking either serotonin reuptake inhibitors or dual serotonin/norepinephrine reuptake inhibitors, whereas seven were not.

All healthy controls were (1) female; (2) right handed; (3) between the ages of 18 and 60; and (4) had no chronic medical illnesses.

Neuroimaging

Image acquisition. PET scans were acquired with a Siemens (Knoxville, TN) HR^+ scanner in three-dimensional mode [reconstructed full-width at half-maximum (FWHM) resolution, ~5.5 mm in-plane and 5.0 mm axially], with septa retracted and scatter correction. Participants were positioned in the PET scanner gantry, and an intravenous (antecubital) line was placed in the right arm. A light forehead restraint was used to eliminate intrascan head movement. [^{11}C]carfentanil was synthesized at high specific activity (>2000 Ci/mmol) by the reaction of [^{11}C]methyliodide and a nonmethyl precursor as described previously (Dannals et al., 1985), with minor modifications to improve its synthetic yield (Jewett, 2001); 10–15 mCi (370–555 MBq) were administered during the scan. Receptor occupancy by carfentanil was calculated to be between 0.2 and 0.6% for brain regions with low, intermediate, and high MOR concentrations, based on the mass of carfentanil administered and the known concentration of opioid receptors in the postmortem human brain (Gross-Isseroff et al., 1990; Gabilondo et al., 1995). Fifty percent of the [^{11}C]carfentanil dose was administered as a bolus, and the remaining 50% was administered by continuous infusion for the remainder of the study. Twenty-eight frames of images were acquired over 90 min with an increasing duration (30 s up to 10 min).

Anatomical magnetic resonance imaging (MRI) scans were acquired in all subjects on a 3 tesla scanner (Signa LX; General Electric, Milwaukee, WI). Acquisition sequences were axial SPGR IR-Prep magnetic resonance (MR) (echo time, 3.4 ms; repetition time, 10.5 ms; inversion time, 200 ms; flip angle, 20°; number of excitations, 1; number of contiguous images, 124; thickness, 1.5 mm).

Image processing. PET images were reconstructed using iterative algorithms (brain mode; FORE/OSEM, four iterations, 16 subsets; no smoothing) into a 128 × 128 pixel matrix in a 28.8 cm diameter field of view. Attenuation correction was performed through a 6 min transmission scan (^{68}Ge source) obtained before the PET study and with iterative reconstruction of the blank/transmission data followed by segmentation of the attenuation image. Small head motions during emission scans were corrected by an automated computer algorithm for each subject before analysis, and the images were coregistered to each other with the same software (Minoshima et al., 1993). Time points were then decay corrected during reconstruction of the PET data. Image data were transformed on a voxel-by-voxel basis into two sets of parametric maps: (1) a tracer transport measure (K_1 ratio) and (2) a receptor-related measure at equilibrium [distribution volume ratio (DVR)]. To avoid the need for arterial blood sampling, the tracer transport and binding measures were calculated using a modified Logan graphical analysis (Logan et al., 1996), using the occipital cortex (an area devoid of MORs) as the reference region. The slope of the Logan plot was used for the estimation of the DVR, a measure equal to the $(f_2B_{max}/K_d) + 1$ for this receptor site and radiotracer. f_2B_{max}/K_d (or DVR − 1) is the receptor-related measure (BP or MOR availability). The term f_2 refers to the concentration of free radiotracer in the extracellular fluid and is considered to represent a constant and very small value. K_1 and DVR images for each experimental period and MR images were coregistered to each other and to the International Consortium for Brain Mapping (ICBM) stereotactic atlas orientation. The accuracy of coregistration and nonlinear warping algorithms was confirmed for each subject individually by comparing the transformed MRI and PET images to each other and the ICBM atlas template.

Group differences were mapped into stereotactic space using *t* maps of statistical significance with SPM2 (Wellcome Department of Cognitive Neurology, London, UK) and Matlab (MathWorks, Natick, MA) software, with a general linear model. No global normalization was applied to the data, and therefore the calculations presented are based on absolute f_2B_{max}/K_d estimates. Only regions with specific MOR BP were included in the analyses (i.e., voxels with DVR values >1.1). To compensate for small residual anatomic variations across subjects and to improve signal-to-noise ratios, a three-dimensional Gaussian filter (FWHM, 6 mm) was applied to each scan.

Image analysis. The comparisons between patients and control subjects were performed using two-sample *t* tests, on a voxel-by-voxel basis within SPM2. Significant effects were detected using a statistical threshold that controls a type I error rate at $p = 0.05$, corrected for multiple comparisons. These statistical thresholds were estimated using the Euler characteristic (Worsley et al., 1992) based on the number of voxels in the gray matter and image smoothness and the extent of local changes (correction for cluster volume) (Friston et al., 1991). Correlations between MOR BP and the relative amount of the affective quality of clinical pain were made using a regression model on a voxel-by-voxel basis with SPM2. Significant effects were detected using a cluster-corrected threshold *p* value of 0.05.

Numerical values for MOR binding were extracted from the image data by averaging the values of voxels contained in the area in which significant effects were obtained in the analyses. These values were then entered into SPSS version 14.0 (SPSS, Chicago, IL) for plotting, to rule out the presence of outliers, and to perform correlations with clinical measures.

Global BP values were also extracted and compared between groups with Student's *t* test. Because global values were found to be lower in the patients (see Results), global values were used as a covariate in regression analyses in which MOR BP was used as the dependent variable and group status and global BP were independent variables. This allows an estimate of group differences for a specific region, while controlling for differences

in global scores. To examine effects of concomitant drug usage in the patients, additional regression analyses were performed in which MOR BP was again used as the dependent variable and clinical pain and drug usage (either taking or not taking reuptake inhibitors; see above) were added as covariates. This final procedure was used to examine the effect of drug usage in the patient group on the relationship between MOR BP and pain.

Clinical assessment

Clinical pain. Clinical pain was assessed immediately before the PET scan with the Short Form of the McGill Pain Questionnaire (SF MPQ) (Melzack, 1987). The SF MPQ has two subscales that measure "sensory" and "affective" qualities of pain. To assess the relative contribution of the affective dimension of pain, the affective subscore of the SF MPQ was divided by the sensory subscore (affective/sensory). This yields an estimate of the relative contribution of the affective component of pain while controlling for the sensory intensity of the sensation (Petzke et al., 2005). For comparison, we also calculated the ratio of the sensory versus the affective subscores of the SF MPQ (i.e., sensory/affective).

Psychological assessment. Depressive symptoms were assessed with the Center for Epidemiological Studies-Depression Scale (Radloff, 1977). This is a 20-item self-report instrument that was developed by the National Institute of Mental Health to detect major or clinical depression in adolescents and adults in both clinical and normal populations. The total score was used for correlation with MOR BP.

Results

As expected, no significant differences were observed between the FM group and the control group with respect to participant age or sex (all $p > 0.05$). During PET imaging, FM patients exhibited significant reductions in MOR BP compared with controls in four regions: the bilateral nucleus accumbens (NAc; left, $p < 0.02$; right, $p < 0.05$; corrected for multiple comparisons), the left amygdala ($p < 0.05$; corrected for multiple comparisons), and the right dorsal anterior cingulate ($p < 0.05$; corrected for multiple comparisons) (Fig. 1*A–C*; Table 1). Global mean MOR BP values were reduced in the patient group ($p < 0.01$). Because a reduction in global BP value could explain the lower BP values within these regions for the FM participants, we performed regression analyses using regional MOR BP values as the dependent variable and group assignment and global BP as covariates. Both the left ($p < 0.001$) and right ($p < 0.05$) nucleus accumbens and the amygdala ($p < 0.005$) showed reduced MOR BP in the patients after controlling for global BP differences. The dorsal anterior cingulate showed a trend toward significance ($p < 0.07$). These data suggest that FM patients have reduced MOR BP within multiple brain regions.

To assess whether drug usage within the FM participants could be responsible for reduced MOR BP values, we examined the mean MOR BP for each of the above regions in FM participants that were either taking or not taking serotonin reuptake inhibitors or dual serotonin/norepinephrine reuptake inhibitors. No differences in BP were detected for any of these regions between patients that were either taking or not taking this class of drugs (all $p > 0.35$). These analyses suggest that the reduced binding observed in the patients for these regions is not attributable to medication usage.

Within the FM patients, MOR BP binding in the left NAc was negatively correlated with clinical pain ratings in the affective (Fig. 2) (SF MPQ affective score, $r = -0.53$; $p < 0.05$) but not the sensory (SF MPQ sensory score, $r = -0.13$; $p > 0.50$) dimension of pain. Drug usage, when added as a covariate, did not significantly alter this relationship (standardized β without drug covariate $= -0.44$; with drug covariate, $\beta = -0.45$; significance of difference, $p = 0.59$). No statistically significant correlations were observed between clinical pain ratings and the right accumbens, the left amygdala, or the right dorsal anterior cingulate BP of FM patients (all $p > 0.05$). A significant negative correlation between MOR BP and depressive symptoms was also observed within the amygdala (Table 2).

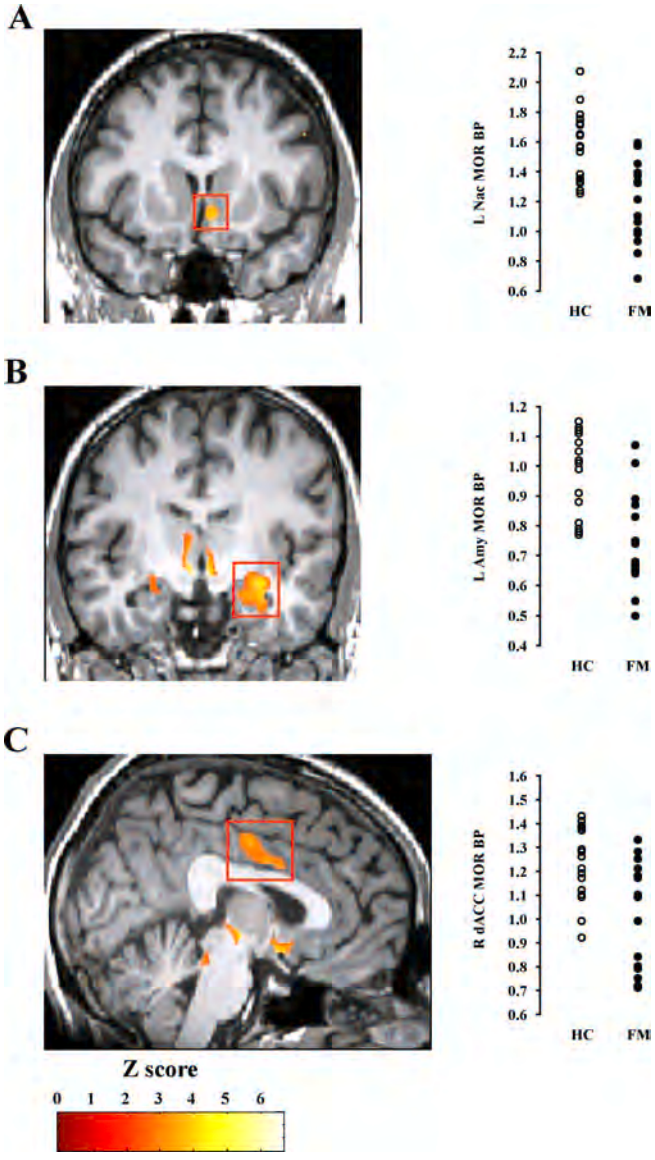


Figure 1. Reduced MOR BP in FM patients. ***A–C***, Regions showing reduced MOR BP: left NAc (L Nac; ***A***), left amygdala (L Amy; ***B***), and right dACC (R dACC; ***C***). Plots of individual MOR BP values extracted from PET images are depicted to the right of each corresponding region of interest. FM and healthy control (HC) participants are shown in black and white circles, respectively.

Because MOR BP within the accumbens was associated with the affective dimension of pain, more so than the sensory dimension, we next investigated the relationship between MOR BP and the relative amount of affective versus sensory pain (SF MPQ, affective score/sensory score). Interindividual differences in MOR binding throughout the cingulate [dorsal anterior (dACC), $p < 0.05$; posterior (pCC), $p < 0.001$; and, to a lesser extent, anterior (aCC), $p = 0.09$; all corrected for multiple comparisons] were negatively correlated with the relative amount of affective pain (Fig. 3*A*,*B*, Table 3). Similar findings were detected within the right ventral putamen (Fig.

Table 1. Regions of reduced [^{11}C]carfentanil binding in FM patients

Brain region	MNI coordinates (*x*, *y*, *z*)	*Z*	Cluster size (mm^3)	%Δ Binding potential (HC − FM; mean ± SD)
NAc (l)	9, 7, −11	4.1*	159	24.7 ± 15.3
NAc (r)	−18, 6, −12	3.3*	140	18.1 ± 13.3
Amygdala (l)	29, −10, −13	3.7*	269	23.7 ± 14.6
dACC (r)	−4, −11, 43	3.1*	182	17.7 ± 12.5

*$p < 0.05$, corrected. MNI, Montreal Neurological Institute; l, left; r, right.

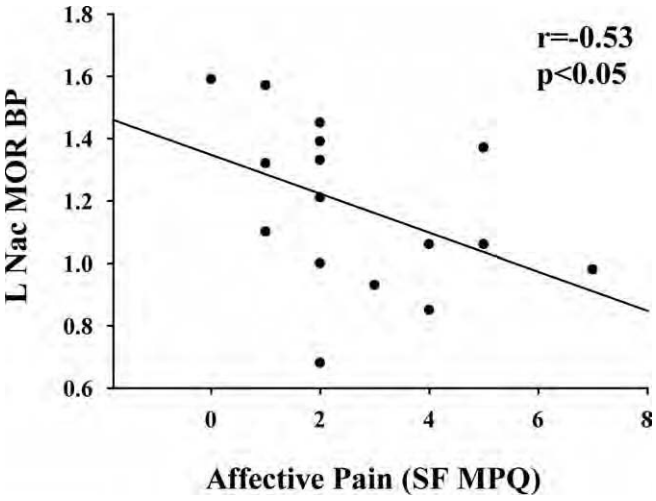


Figure 2. MOR BP is negatively correlated with affective pain. The scatter plot of left accumbens (L Nac) MOR BP and clinical pain (SF MPQ, affective score) reveals a significant negative correlation ($r = -0.53$; $p < 0.05$).

Table 2. Correlations between MOR availability and depression ratings in FM

Brain region	*Rho* value
NAc (l)	−0.25
NAc (r)	0.16
Amygdala (l)	−0.49*
dACC (r)	−0.21

*$p < 0.05$. l, Left; r, right.

3*C*). The primary somatosensory cortex and the insula also showed a negative correlation with MOR BP; however, these regions did not reach significance after correction for multiple comparisons ($p > 0.05$). Adding medication usage as a covariate did not significantly alter the relationship between affective/sensory scores and MOR BP for any of these regions (all percentage differences in standardized βs with and without covariate $\leq$ 1.3%; all significance of change, $p > 0.20$). No significant negative correlations were observed between MOR BP and the relative amount of sensory pain (SF MPQ, sensory score/affective score) within any brain regions (all $p > 0.05$). No correlations were observed between MOR BP within any of these regions and depressive symptoms (all $p > 0.20$). These results suggest that in FM patients the affective quality of pain is associated with reduced MOR availability throughout the cingulate and other brain regions commonly associated with pain modulation.

Discussion

Our data indicate that FM patients have reduced MOR BP within structures typically observed in imaging studies of experimental pain involving healthy control participants. These structures include the amygdala, the cingulate, and the nucleus accumbens.

All of these regions have previously been noted to play some role in nociception and pain. Opioid activity in the nucleus accumbens and the amygdala has been shown to modulate nociceptive neural transmission in animal models of pain (Gear and Levine, 1995; Manning, 1998). Indeed, endogenous opioids play a central role in analgesia and the perception of painful stimuli (Fields, 2004). MOR-mediated neurotransmission in the nucleus accumbens and amygdala has also been shown to be modulated by pain in healthy controls reducing the pain experience (Zubieta et al., 2001), in a manner consistent with animal data. Because the concentration of endogenous opioids is elevated in the CSF of FM patients (Baraniuk et al., 2004), MORs may be highly occupied by endogenous ligand in an attempt to reduce pain or downregulated after prolonged stimulation. Both these effects could explain the reduced MOR BP observed in this study.

An investigation using functional magnetic resonance imaging (fMRI) in FM has associated enhanced neural activity in both the amygdala and the cingulate with depressive symptoms (Giesecke et al., 2005). This further supports the notion that these regions may be involved with evaluating affective aspects of pain and is consistent with our findings of reduced MOR BP within the amygdala and its correlation with depressive symptoms. Indeed, the dorsal anterior cingulate region, identified as having reduced MOR BP in the patients, also showed a negative correlation with the affective dimension of pain (albeit in the opposite hemisphere). These data suggest that MOR availability within the dorsal anterior cingulate is related to the affective dimension of pain. This finding is supported by previous imaging studies of the cingulate (Vogt, 2005).

Two other chronic pain states, rheumatoid arthritis (Jones et al., 1994) and central neuropathic pain following stroke (Jones et al., 2004; Willoch et al., 2004), also display a reduction in opioid receptor BP within the CNS, as measured with the nonselective opioid receptor radiotracer [^{11}C]diprenorphine. Although these data may then suggest that reduced opioid receptor availability may be a shared feature across chronic pain states, the regional distribution of reduced receptor binding was dissimilar across these studies and pain conditions. In rheumatoid arthritis pain, reduced opioid receptor binding was observed in the cingulate, frontal, and temporal cortices, whereas for central neuropathic pain, reduced opioid receptor availability was detected primarily within the thalamus, somatosensory cortex, cingulate, and insula. In patients with peripheral neuropathic pain, reduced opioid BP has been observed bilaterally across brain hemispheres, whereas in central neuropathic pain, reductions in BP were observed largely isolated to one hemisphere (Maarrawi et al., 2007). This heterogeneous pattern of reduced binding may reflect different underlying mechanisms operating in these diverse pain conditions. In the case of FM the reductions in MOR BP observed were localized in regions known to be involved in antinociception in animal models (Gear and Levine, 1995; Manning,

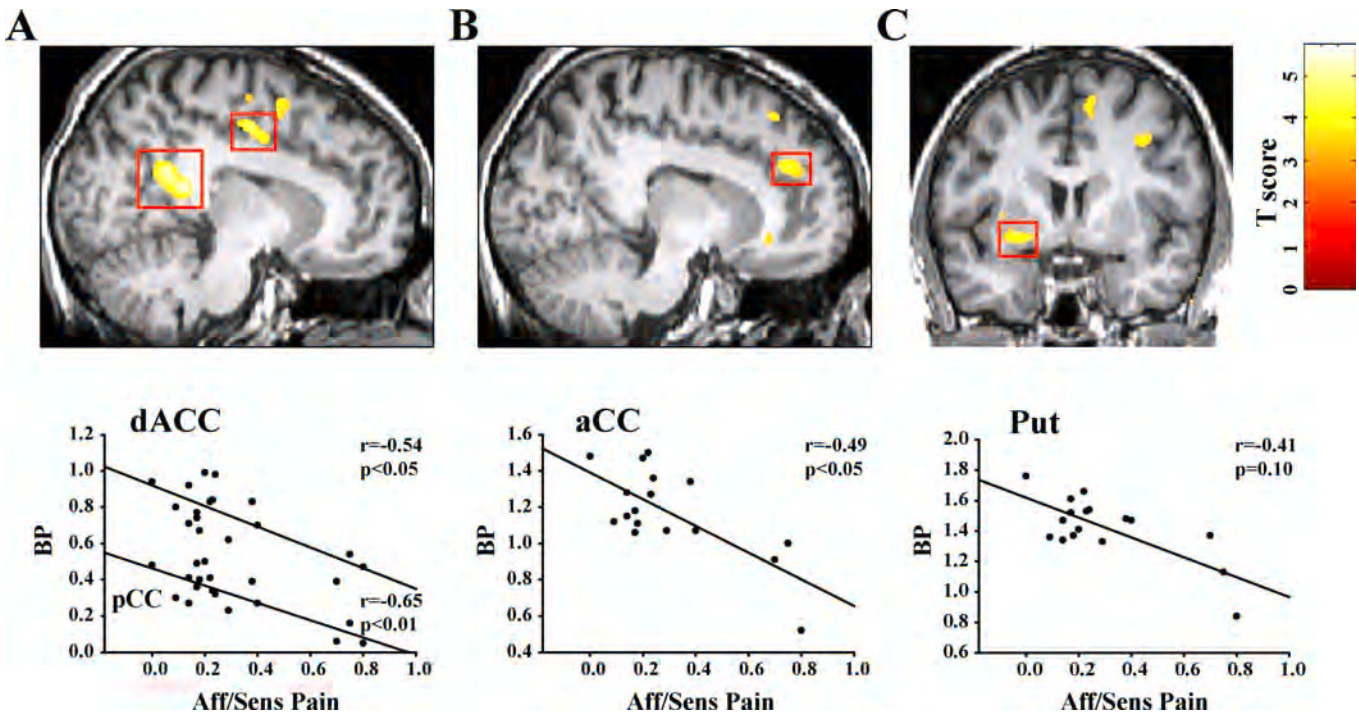


Figure 3. Relative magnitude of the affective pain dimension is associated with reduced MOR BP throughout the cingulate and striatum in FM. ***A–C***, Regions showing significant correlations with SF MPQ affective/sensory (Aff/Sens) scores: left dACC and pCC (***A***), right aCC (***B***), and right putamen (Put; ***C***). Scatter plots of individual MOR BP values extracted from PET images are plotted against affective/sensory scores below each image.

Table 3. Regions of correlated MOR BP and relative amount of affective versus sensory pain

Brain region	MNI coordinates (*x*, *y*, *z*)	*Z*	Cluster size (mm^3)	*Rho* value for extracted ROIs
dACC (l)	10, −11, 48	3.75**	1001	−0.54
pCC (l)	10, −44, 17	4.11***	936	−0.65
aCC (r)	−12, 38, 28	3.44*	410	−0.49
Putamen (r)	−26, 4, −8	3.36**	517	−0.41

*$p = 0.09$, corrected; **$p < 0.05$, corrected; ***$p < 0.001$, corrected. MNI, Montreal Neurological Institute; ROIs, regions of interest.

1998), as well as pain and emotion regulation, including the affective quality of pain, in humans (Rainville et al., 1997; Zubieta et al., 2001, 2003) (i.e., dorsal anterior cingulate, nucleus accumbens, and amygdala).

Prolonged activations of the MOR by sustained elevations of endogenous agonist have been shown to result in a subsequent decrease in the concentration of MORs in animal models of chronic pain (Li et al., 2005). Chronic administration of morphine may reduce MOR functioning possibly by altering the ability of the receptor to bind to G-proteins, whereas other agonists also downregulate and internalize these receptors (Whistler et al., 1999). If this were the case in FM, sustained activation of MORs by endogenous agonists could ultimately lead to a downregulation of MOR receptor concentration, function, or both. Therefore both mechanisms (i.e., increased release of endogenous opioids and/or a reduction in receptor function) could be responsible for our findings.

We also observed a negative correlation between MOR BP within the accumbens and clinical ratings in the affective dimension of pain. This supports the hypothesis that mechanisms of clinical FM pain are coupled to MOR availability. A strong relationship between pain affect and MOR BP was also observed throughout multiple regions of the cingulate. This is consistent with a proposed role of the dorsal and anterior cingulate in the modulation of pain perception via opioidergic mechanisms (Vogt et al., 1995). Recent investigations of opioid receptor binding in healthy controls showed reduced receptor availability within the rostral cingulate during thermal pain (Sprenger et al., 2006) and sustained muscular pain, which correlated with the suppression of pain affect (Zubieta et al., 2001). Within animal models of experimental pain, microinjection of morphine into the anterior cingulate dose-dependently reduced affective components of pain greater than sensory aspects (LaGraize et al., 2006). Our findings of greater affective pain associated with lower MOR BP within the cingulate are consistent with these observations.

We also detected a negative correlation between affective pain and MOR BP values within the posterior cingulate. This is potentially a novel finding because this region is not typically observed in pain imaging trials in humans (Vogt, 2005). However previous trials do suggest that activity within the posterior cingulate, specifically the dorsal aspect, is related to skeletomotor orientation of the body in response to noxious stimuli (Vogt, 2005; Vogt and Laureys, 2005). Because our FM participants experienced clinical pain during the scanning sessions, one could speculate that reduced MOR BP within this region may reflect activation of the endogenous opioid system in an attempt to reduce skeletomotor orientation resulting from spontaneous clinical pain. One additional potential lim-

itation of this final analysis is that affective and sensory pain dimensions are often highly correlated.

A significant relationship was also detected between MOR availability within the amygdala and depression. Individuals with more depressive symptoms had reductions in MOR BP within the amygdala. This finding is not unexpected, because reduced opioid receptor availability within the amygdala has been previously associated with periods of sadness in patients with major depressive disorder (Kennedy et al., 2006).

Perhaps more important for clinical investigations in FM, our results would predict a lack of efficacy for exogenous opioids in this population. Regardless of whether endogenous opioids are high (Baraniuk et al., 2004) or MORs are downregulated, both scenarios would predict that FM patients would respond less well to exogenous opioids. This prediction awaits future prospective trials of exogenous opioid treatments in FM.

Overall we detect decreased MOR availability in FM patients, demonstrating a dysregulation of this neurotransmitter system in this disease. The reduction in binding was further negatively correlated with affective pain. The observation of specific regional alterations in central opioid neurotransmission in FM suggests that these mechanisms, possibly as a consequence of persistent pain, are involved in the clinical presentation and even the perpetuation of symptoms in this illness. Furthermore, because these receptors are the target of opiate drugs, a profound reduction in the concentration or function of these receptors is consistent with a poor response of FM patients to this class of analgesics, observed anecdotally in clinical settings.

References

Baraniuk JN, Whalen G, Cunningham J, Clauw DJ (2004) Cerebrospinal fluid levels of opioid peptides in fibromyalgia and chronic low back pain. BMC Musculoskelet Disord 5:48.

Clauw DJ, Chrousos GP (1997) Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 4:134–153.

Cohen ML (1999) Is fibromyalgia a distinct clinical entity? The disapproving rheumatologist's evidence. Baillieres Best Pract Res Clin Rheumatol 13:421–425.

Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH (2004) Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol 31:364–378.

Dannals RF, Ravert HT, Frost JJ, Wilson AA, Burns HD, Wagner Jr HN (1985) Radiosynthesis of an opiate receptor binding radiotracer: [11C]carfentanil. Int J Appl Radiat Isot 36:303–306.

Fields H (2004) State-dependent opioid control of pain. Nat Rev Neurosci 5:565–575.

Friston KJ, Frith CD, Liddle PF, Frackowiak RS (1991) Comparing functional (PET) images: the assessment of significant change. J Cereb Blood Flow Metab 11:690–699.

Gabilondo AM, Meana JJ, Garcia-Sevilla JA (1995) Increased density of mu-opioid receptors in the postmortem brain of suicide victims. Brain Res 682:245–250.

Gear RW, Levine JD (1995) Antinociception produced by an ascending spino-supraspinal pathway. J Neurosci 15:3154–3161.

Giesecke T, Williams DA, Harris RE, Cupps TR, Tian X, Tian TX, Gracely RH, Clauw DJ (2003) Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. Arthritis Rheum 48:2916–2922.

Giesecke T, Gracely RH, Williams DA, Geisser M, Petzke F, Clauw DJ (2005) The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. Arthritis Rheum 52:1577–1584.

Gracely RH, Petzke F, Wolf JM, Clauw DJ (2002) Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 46:1333–1343.

Gross-Isseroff R, Dillon KA, Israeli M, Biegon A (1990) Regionally selective increases in mu opioid receptor density in the brains of suicide victims. Brain Res 530:312–316.

Jewett DM (2001) A simple synthesis of [11C]carfentanil using an extraction disk instead of HPLC. Nucl Med Biol 28:733–734.

Jones AK, Cunningham VJ, Ha-Kawa S, Fujiwara T, Luthra SK, Silva S, Derbyshire S, Jones T (1994) Changes in central opioid receptor binding in relation to inflammation and pain in patients with rheumatoid arthritis. Br J Rheumatol 33:909–916.

Jones AK, Watabe H, Cunningham VJ, Jones T (2004) Cerebral decreases in opioid receptor binding in patients with central neuropathic pain measured by [11C]diprenorphine binding and PET. Eur J Pain 8:479–485.

Julien N, Goffaux P, Arsenault P, Marchand S (2005) Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 114:295–302.

Kennedy SE, Koeppe RA, Young EA, Zubieta JK (2006) Dysregulation of endogenous opioid emotion regulation circuitry in major depression in women. Arch Gen Psychiatry 63:1199–1208.

LaGraize SC, Borzan J, Peng YB, Fuchs PN (2006) Selective regulation of pain affect following activation of the opioid anterior cingulate cortex system. Exp Neurol 197:22–30.

Li Z, Proud D, Zhang C, Wiehler S, McDougall JJ (2005) Chronic arthritis down-regulates peripheral mu-opioid receptor expression with concomitant loss of endomorphin 1 antinociception. Arthritis Rheum 52:3210–3219.

Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL (1996) Distribution volume ratios without blood sampling from graphical analysis of PET data. J Cereb Blood Flow Metab 16:834–840.

Lorenz J, Grasedyck K, Bromm B (1996) Middle and long latency somatosensory evoked potentials after painful laser stimulation in patients with fibromyalgia syndrome. Electroencephalogr Clin Neurophysiol 100:165–168.

Maarrawi J, Peyron R, Mertens P, Costes N, Magnin M, Sindou M, Laurent B, Garcia-Larrea L (2007) Differential brain opioid receptor availability in central and peripheral neuropathic pain. Pain 127:183–194.

Manning BH (1998) A lateralized deficit in morphine antinociception after unilateral inactivation of the central amygdala. J Neurosci 18:9453–9470.

Melzack R (1987) The short-form McGill Pain Questionnaire. Pain 30:191–197.

Minoshima S, Koeppe RA, Mintun MA, Berger KL, Taylor SF, Frey KA, Kuhl DE (1993) Automated detection of the intercommissural line for stereotactic localization of functional brain images. J Nucl Med 34:322–329.

Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH (2003) Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. Pain 105:403–413.

Petzke F, Harris RE, Williams DA, Clauw DJ, Gracely RH (2005) Differences in unpleasantness induced by experimental pressure between patients with fibromyalgia and controls. Eur J Pain 9:325–335.

Radloff LS (1977) The CES-D Scale: a self-report depression scale for research in the general population. Applied Psychological Measurement 1:385–401.

Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC (1997) Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277:968–971.

Rao SG, Clauw DJ (2004) The management of fibromyalgia. Drugs Today (Barc) 40:539–554.

Russell IJ, Vaeroy H, Javors M, Nyberg F (1992) Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. Arthritis Rheum 35:550–556.

Sprenger T, Valet M, Boecker H, Henriksen G, Spilker ME, Willoch F, Wagner KJ, Wester HJ, Tolle TR (2006) Opioidergic activation in the medial pain system after heat pain. Pain 122:63–67.

Vogt BA (2005) Pain and emotion interactions in subregions of the cingulate gyrus. Nat Rev Neurosci 6:533–544.

Vogt BA, Laureys S (2005) Posterior cingulate, precuneal and retrosplenial cortices: cytology and components of the neural network correlates of consciousness. Prog Brain Res 150:205–217.

Vogt BA, Wiley RG, Jensen EL (1995) Localization of mu and delta opioid receptors to anterior cingulate afferents and projection neurons and input/output model of mu regulation. Exp Neurol 135:83–92.

Whistler JL, Chuang HH, Chu P, Jan LY, von Zastrow M (1999) Functional dissociation of mu opioid receptor signaling and endocytosis: implica-

tions for the biology of opiate tolerance and addiction. Neuron 23:737–746.

Willoch F, Schindler F, Wester HJ, Empl M, Straube A, Schwaiger M, Conrad B, Tolle TR (2004) Central poststroke pain and reduced opioid receptor binding within pain processing circuitries: a [11C]diprenorphine PET study. Pain 108:213–220.

Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P (1990) The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 33:160–172.

Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L (1995) The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 38:19–28.

Woolf CJ (2004) Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 140:441–451.

Worsley KJ, Evans AC, Marrett S, Neelin P (1992) A three-dimensional statistical analysis for CBF activation studies in human brain. J Cereb Blood Flow Metab 12:900–918.

Zubieta JK, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM, Meyer CR, Koeppe RA, Stohler CS (2001) Regional mu opioid receptor regulation of sensory and affective dimensions of pain. Science 293:311–315.

Zubieta JK, Ketter TA, Bueller JA, Xu Y, Kilbourn MR, Young EA, Koeppe RA (2003) Regulation of human affective responses by anterior cingulate and limbic mu-opioid neurotransmission. Arch Gen Psychiatry 60:1145–1153.

ARTHRITIS & RHEUMATISM
Vol. 60, No. 10, October 2009, pp 3146–3152
DOI 10.1002/art.24849

Elevated Insular Glutamate in Fibromyalgia Is Associated With Experimental Pain

Richard E. Harris,[1] Pia C. Sundgren,[1] A. D. Craig,[2] Eric Kirshenbaum,[1] Ananda Sen,[1] Vitaly Napadow,[3] and Daniel J. Clauw[1]

Objective. **Central pain augmentation resulting from enhanced excitatory and/or decreased inhibitory neurotransmission is a proposed mechanism underlying the pathophysiology of functional pain syndromes such as fibromyalgia (FM). Multiple functional magnetic resonance imaging studies implicate the insula as a region of heightened neuronal activity in this condition. Since glutamate (Glu) is a major cortical excitatory neurotransmitter that functions in pain neurotransmission, we undertook this study to test our hypothesis that increased levels of insular Glu would be present in FM patients and that the concentration of this molecule would be correlated with pain report.**

Methods. **Nineteen FM patients and 14 age- and sex-matched pain-free controls underwent pressure pain testing and a proton magnetic resonance spectroscopy session in which the right anterior insula and right posterior insula were examined at rest.**

Results. **Compared with healthy controls, FM patients had significantly higher levels of Glu (mean ± SD 8.09 ± 0.72 arbitrary institutional units versus 6.86 ± 1.29 arbitrary institutional units; $P = 0.009$) and combined glutamine and Glu (i.e., Glx) (mean ± SD 12.38 ± 0.94 arbitrary institutional units versus 10.59 ± 1.48 arbitrary institutional units; $P = 0.001$) within the right posterior insula. No significant differences between groups were detected in any of the other major metabolites within this region ($P > 0.05$ for all comparisons), and no group differences were detected for any metabolite within the right anterior insula ($P > 0.11$ for all comparisons). Within the right posterior insula, higher levels of Glu and Glx were associated with lower pressure pain thresholds across both groups for medium pain (for Glu, $r = -0.43$, $P = 0.012$; for Glx, $r = -0.50$, $P = 0.003$).**

Conclusion. **Enhanced glutamatergic neurotransmission resulting from higher concentrations of Glu within the posterior insula may play a role in the pathophysiology of FM and other central pain augmentation syndromes.**

Although acute pain can function beneficially to alert an organism to immediate or imminent tissue damage, chronic pain can often occur in the absence of tissue damage or inflammation. Functional chronic pain syndromes are a subset of pain disorders in which patients paradoxically report frequent pain symptoms in the absence of anatomic injury or objective pathologic findings (1,2). As such, these disorders are particularly troublesome for patients and clinicians alike. Although new treatment options exist (3–5), significant disability and dysfunction are prevalent.

Fibromyalgia (FM) is the prototypical functional

ClinicalTrials.gov identifier: NCT00142597.

Supported by the US Department of the Army (grant DAMD-W81XWH-07-2-0050), the NIH (National Center for Research Resources grant M01-RR-000042), and the Dana Foundation (Award in Brain and Immuno-Imaging). Dr. Harris' work was supported by the NIH (National Center for Complementary and Alternative Medicine grant K01-AT-01111-01). Dr. Napadow's work was supported by the NIH (National Center for Complementary and Alternative Medicine grants K01-AT-002166, R01-AT-004714, and P01-AT-002048).

[1]Richard E. Harris, PhD, Pia C. Sundgren, MD, PhD, Eric Kirshenbaum, BS, Ananda Sen, PhD, Daniel J. Clauw, MD: University of Michigan, Ann Arbor; [2]A. D. Craig, PhD: Barrow Neurological Institute, Phoenix, Arizona; [3]Vitaly Napadow, PhD: Massachusetts General Hospital, Charlestown.

Dr. Harris has received consulting fees, speaking fees, and/or honoraria from Pfizer (less than $10,000). Dr. Napadow has received consulting fees, speaking fees, and/or honoraria from Boston University (less than $10,000). Dr. Clauw has received consulting fees, speaking fees, and/or honoraria from Pfizer, UCB, Wyeth, and Cypress Bioscience (less than $10,000 each) and from Pierre Fabre Laboratories, Lilly, and Forest Laboratories (more than $10,000 each), as well as a one-time royalty from Lilly for the knowfibro.com Web site.

Address correspondence and reprint requests to Richard E. Harris, PhD, University of Michigan, Chronic Pain and Fatigue Research Center, 24 Frank Lloyd Wright Drive, PO Box 385, Lobby M, Ann Arbor, MI 48106. E-mail: reharris@med.umich.edu.

Submitted for publication March 31, 2009; accepted in revised form June 23, 2009.

chronic pain condition, and it affects ~2–4% of individuals (6–8). Although the etiology of this disorder remains largely unknown, emerging data suggest that FM arises through augmentation of central pain processing pathways. This hypothesis is based largely upon findings of previous functional neuroimaging studies showing that FM patients display augmented neuronal responses to both innocuous and painful stimuli (9,10), corroborating the allodynia and hyperalgesia seen in this condition (11).

A growing body of literature suggests that glutamate (Glu), an excitatory neurotransmitter, within the central nervous system may play a role in FM pathology. A study by Peres et al found that cerebrospinal fluid (CSF) levels of Glu were elevated in FM patients, possibly having consequences for glutamatergic neurotransmission (12). In a separate line of inquiry, the concentration of glutamine (Gln; a precursor in Glu biosynthesis) in the CSF of FM patients was positively correlated with a number of evoked pain measures—greater Gln levels were associated with greater pain (13). Moreover, administration of ketamine, a Glu channel blocker, has been found to reduce experimental (14) and clinical (15) pain in FM. While these studies are informative, they do not identify a specific brain region(s) that is either the origin or the target of Glu in FM.

We recently demonstrated that long-term treatment of FM patients with acupuncture and/or sham acupuncture led to changes in Glu levels within the posterior insula that were correlated with changes in experimental and clinical pain (16). Patients displaying greater reductions in Glu also had greater decreases in both experimental and clinical pain.

In the present study, we extend these findings by investigating the relationship between insular Glu and combined Gln and Glu (i.e., Glx) in individuals with FM and in age- and sex-matched pain-free controls. We hypothesized that if insular hyperactivity is due to enhanced glutamatergic neurotransmission in FM, patients should display elevated levels of Glu as compared with controls. Furthermore, if these levels are indicative of augmented pain processing, Glu and Glx levels should be negatively correlated with evoked pressure pain thresholds.

PATIENTS AND METHODS

Participants. We studied 19 female FM patients (mean ± SD age 45.2 ± 15.0 years) and 14 age- and sex-matched healthy controls (mean ± SD age 45.9 ± 11.1 years) ($P = 0.89$). All participants gave written informed consent, and all study protocols were approved by the University of Michigan Institutional Review Board.

All participants with FM fulfilled the following conditions: 1) met the American College of Rheumatology (ACR) 1990 criteria for the classification of FM (17) for at least 1 year, 2) had continued presence of pain for >50% of days, 3) were willing to limit the introduction of any new medications or treatment modalities for control of FM symptoms during the study, 4) were >18 years old and <75 years old, 5) were female, 6) were right-handed, and 7) were capable of giving written informed consent. FM participants were excluded if they 1) currently used or had a history of use of opioid or narcotic analgesics; 2) had a history of substance abuse; 3) had the presence of concurrent autoimmune or inflammatory disease, such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, etc., that causes pain; 4) were concurrently participating in other therapeutic trials; 5) were pregnant and/or nursing mothers; 6) had severe psychiatric illnesses (current schizophrenia, major depression with suicidal ideation, substance abuse within the previous 2 years); or 7) had current major depression. A list of concomitant medications for FM participants is available at http://www.med.umich.edu/painresearch/about/Supplementary%20Table%201%20Concurrent%20Medications%20for%20FM%20Participants.pdf. Longitudinal proton magnetic resonance spectroscopy (H-MRS) data for 10 of the FM patients have been reported previously (16).

All healthy controls were >18 years old and <75 years old, female, capable of giving written informed consent, right-handed, and willing to complete all study procedures. Healthy controls were excluded if they had ever met the ACR 1990 criteria for the classification of FM, had any chronic medical illness including psychiatric disorders (psychosis, schizophrenia, delusional disorder, etc.), or were pregnant.

H-MRS. All subjects underwent conventional magnetic resonance imaging (MRI) of the brain on a 3.0T MR scanner (General Electric Medical Systems, Milwaukee, WI). Single-voxel spectroscopy was performed using the following parameters: point resolved spectroscopy, repetition time 3,000 msec, echo time 30 msec, flip angle 90°, number of excitations 8, field of view 16 cm, with a volume of interest (VOI) of $2 \times 2 \times 3$ cm. During each session, 2 separate single-voxel spectroscopy sequences were performed, once with the VOI placed in the right anterior insula and once in the right posterior insula (Figure 1A). The approximate Montreal Neurological Institute coordinates for the centers of the anterior and posterior voxels were 34,19,0 and 38,–17,8, respectively. These coordinates include regions shown previously to be activated during acute pain (18). Also, functional MRI trials in FM have shown augmented pain activity in these regions (9,10).

Given the time constraints for our H-MRS session, we examined the right insula, since it was contralateral to the location where pain stimuli were previously applied in our group's functional MRI trials of FM (9,16). Participants were at rest during the H-MRS session. The raw data from each single-voxel MR spectroscopy sequence underwent manual postprocessing using H-MRS software (LCModel; Stephen Provencher, Oakville, Ontario, Canada). LCModel uses a linear combination of individual spectra obtained from pure molecular species to fit the experimental spectra (Figure 1B). Values for Glu, Gln, Glx, and other metabolites including

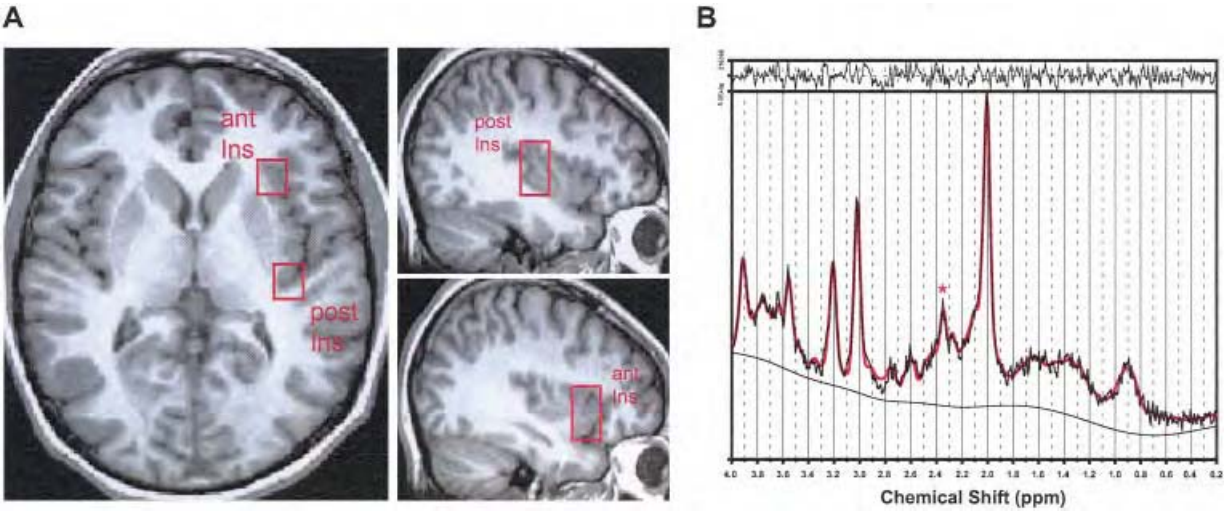


Figure 1. Insula voxel placement and resulting spectrum. **A,** Axial and sagittal T1-weighted images showing single-voxel placements for right anterior insula (ant Ins) and right posterior insula (post Ins). **B,** Representative proton magnetic resonance spectroscopy spectrum from the posterior insula fit with LCModel (red trace; ∗ = resonance from 2 glutamate [Glu] γ proton resonances at 2.35 parts per million [ppm]). LCModel uses a linear combination of individual spectra obtained from pure molecular species to fit the experimental spectra. Absolute concentrations of Glu were calculated in arbitrary institutional units using water as an internal scaling factor.

N-acetylaspartate (NAA), choline compounds, creatine, and *myo*-inositol were calculated as absolute concentrations using the water signal for normalization (19). Resulting metabolite absolute concentrations were reported in arbitrary institutional units.

Since our voxels incorporated CSF, and the volume of CSF dilutes H-MRS–derived metabolite values, we corrected our metabolite levels for CSF volume for each participant. For this we used Voxel Based Morphometry, a toolbox that operates within the image analysis program Statistical Parametric Mapping (SPM; http://www.fil.ion.ucl.ac.uk/spm/software). High-resolution T1-weighted images were segmented into gray matter, white matter, and CSF, and then regions of interest within the anterior and posterior insula were used to extract gray matter, white matter, and CSF volumes from these images using the SPM2 toolbox Marsbar (http://marsbar.sourceforge.net). Metabolite values were corrected by dividing the observed concentration in arbitrary institutional units by the percentage of volume of the entire voxel that was not occupied by CSF (i.e., the percentage of voxel volume occupied by gray matter plus white matter). Corrected metabolite concentrations were entered into SPSS version 16 (SPSS, Chicago, IL) for calculation of differences between FM and healthy control groups and for correlational analyses with pain outcomes.

Experimental pain. Pressure pain tenderness was assessed prior to the H-MRS session as described previously (20,21). Briefly, discrete pressure stimuli were applied to the subject's thumbnail using a stimulation device, which eliminates any direct examiner/subject interaction. Pain intensity ratings were recorded on the Gracely Box Scale (GBS) questionnaire using a random presentation paradigm (21). During the testing, stimulus pressures were determined interactively. A computer program continuously adjusted stimulus pressure levels (low = GBS 0.5, medium = GBS 7.5, high = GBS 13.5) to produce the same response distribution in each subject. Pressure pain thresholds were then correlated with H-MRS–derived metabolite levels using SPSS version 16.

Statistical analysis. Metabolite levels and pain ratings were entered into SPSS version 16. We performed two-way analysis of variance to determine differences in metabolite levels, with group (FM group or healthy control group) and age strata as fixed factors. Since there was evidence of differences in the variability of Glu and Glx levels between the healthy control and FM groups, we performed an additional analysis using weighted least squares, with weights equaling the inverse of the corresponding estimated group variances. We next correlated pressure pain thresholds with Glu and Glx levels from the posterior insula, since these levels were found to be elevated in the FM participants. Pearson's correlations were calculated on the combined group of FM and healthy control participants. Separate multiple linear regression models were constructed with Glu or Glx levels as dependent variables and with group (FM group or healthy control group) medium pressure threshold and age strata as independent variables. *P* values less than 0.05 were considered significant.

RESULTS

FM patients have elevated Glu and Glx levels in the posterior insula. As shown in Table 1 and Figure 2A, compared with healthy controls, individuals with FM displayed elevated levels of both Glu ($P = 0.009$) and Glx ($P = 0.001$) within the posterior insula. Glu and Glx levels remained significantly elevated in similar analyses

Table 1. Comparison of posterior and anterior insula corrected metabolite levels (in arbitrary institutional units) between FM patients and healthy controls*

Location, metabolite	FM patients	Healthy controls	*P*
Posterior insula			
Glu	8.09 ± 0.72	6.86 ± 1.29	0.009
Glx	12.38 ± 0.94	10.59 ± 1.48	0.001
Gln	4.30 ± 0.86	3.73 ± 1.13	0.13
NAA	10.47 ± 0.64	9.46 ± 1.58	0.06
Creatine	7.15 ± 0.78	6.52 ± 1.15	0.10
Myo-inositol	4.94 ± 0.60	4.86 ± 0.98	0.98
Cho	1.81 ± 0.27	1.63 ± 0.37	0.15
Anterior insula			
Glu	9.91 ± 1.47	9.29 ± 1.11	0.52
Glx	14.30 ± 2.48	13.78 ± 1.93	0.85
Gln	4.40 ± 1.82	4.49 ± 1.77	0.82
NAA	12.49 ± 1.77	11.38 ± 1.02	0.12
Creatine	8.29 ± 1.41	7.92 ± 0.88	0.60
Myo-inositol	5.66 ± 1.16	5.74 ± 0.53	0.45
Cho	2.32 ± 0.43	2.21 ± 0.32	0.49

* Values are the mean ± SD. FM = fibromyalgia; Glu = glutamate; Glx = Glu plus glutamine (Gln); NAA = *N*-acetylaspartate; Cho = choline compounds.

that used weighted least squares ($P = 0.008$ for Glu, $P = 0.001$ for Glx). Eighteen of the 19 FM patients had mean Glu levels that were higher than the mean level in healthy controls, whereas all FM patients had higher Glx levels than the mean level in healthy controls. FM patients also had a trend toward higher NAA levels in the posterior insula ($P = 0.06$); however, this did not reach statistical significance. There were no differences between FM and healthy control groups in levels of the other major metabolites (Gln, *myo*-inositol, creatine, and choline compounds) within the posterior insula ($P \geq 0.10$ for all comparisons). These data suggest a relatively specific elevation of Glu and Glx levels in the right posterior insula for the FM group.

As shown in Table 1 and Figure 2B, there were no significant group differences in the levels of Glu and Glx or other metabolites within the anterior insula ($P > 0.11$ for all comparisons). These data suggest that the elevated levels of Glu are specific for the posterior insula and do not extend into the anterior regions.

Glu and Glx levels are negatively correlated with pressure pain thresholds. Significant negative correlations between pressure pain thresholds and posterior insula Glu and Glx levels were observed when both groups were combined (Table 2). A scatterplot of posterior insula Glx values versus medium pressure pain thresholds is illustrated in Figure 3. These data suggest that, regardless of whether an individual is an FM patient or a healthy control, individuals with higher levels of Glu and/or Glx also have enhanced sensitivity to experimentally induced pressure pain.

Since group status (FM group or healthy control group) and pressure pain thresholds were both related to Glu and Glx levels in the posterior insula, we constructed separate linear regression models with either Glu or Glx levels as dependent variables and group (FM group or healthy control group) and medium pressure

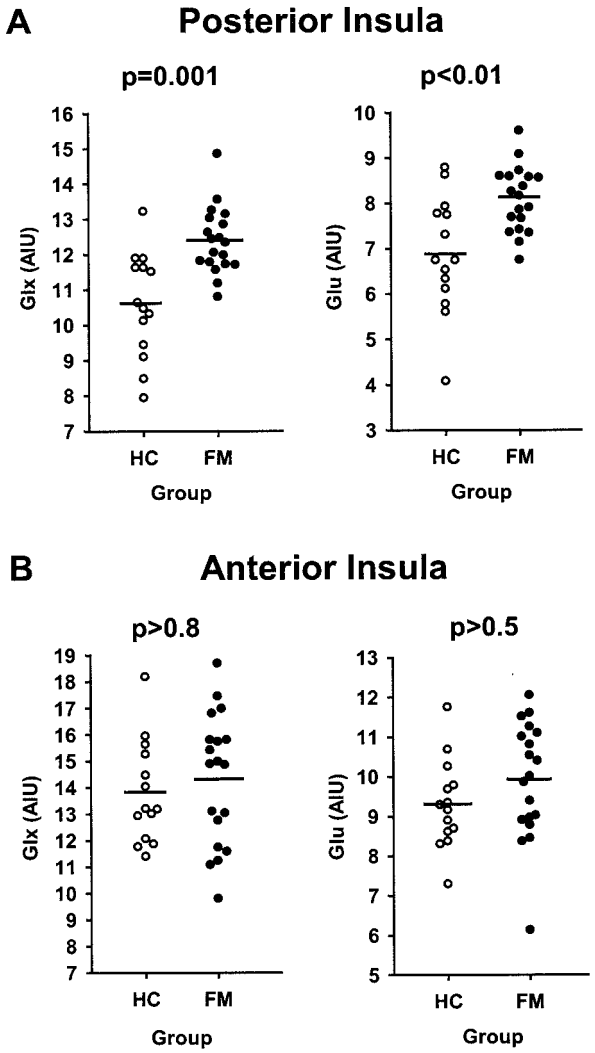


Figure 2. Elevated levels of glutamate (Glu) and combined glutamine and Glu (Glx) within the posterior insula of patients with fibromyalgia (FM). Circles represent corrected Glx and Glu levels in the posterior insula **(A)** and in the anterior insula **(B)** for individual FM patients and healthy controls (HC). Horizontal bars indicate the mean. FM patients have elevated concentrations of Glu and Glx in the posterior insula, while there is no difference between FM patients and healthy controls in Glu and Glx levels in the anterior insula. AIU = arbitrary institutional units.

Table 2. Correlation of posterior insula Glu and Glx levels with pressure pain thresholds in the combined groups of FM patients and healthy controls*

Pressure threshold	Glu		Glx	
	r	*P*	r	*P*
Low pain	−0.53	0.002	−0.55	0.001
Medium pain	−0.43	0.012	−0.50	0.003
High pain	−0.38	0.03	−0.54	0.001

* See Table 1 for definitions.

pain threshold as independent variables. Since the FM patients and healthy controls were matched by age, we further used age as a stratum variable (factor) in the regression model. This is akin to the stratified analysis traditionally carried out in case–control designs.

As shown in Table 3, both group and pressure pain threshold were significant predictors of Glx levels, and these factors showed a trend toward significance for Glu levels. For both Glu and Glx, FM patients exhibited higher values than the controls. For example, the FM patients had on average 1.16 units higher Glx values compared with the healthy controls, for a fixed pressure pain level and age stratum. Further, medium pressure pain threshold was negatively associated with each of the outcomes. No significant group–pressure pain interaction term was detected for either model (both $P > 0.25$), and for this reason, the interaction term was not included in the final models. Similar results were obtained in analyses using weighted least squares (for Glx, group $\beta = 1.28$, $P = 0.009$; medium pressure $\beta = -0.47$, $P = 0.007$ and for Glu, group $\beta = 0.78$, $P = 0.07$; medium pressure $\beta = -0.41$, $P = 0.007$). Similar effects were also obtained when using general linear models with the high pressure threshold (for Glx, group $\beta = 1.23$, $P = 0.01$; high pressure $\beta = -0.37$, $P = 0.008$ and for Glu, group $\beta = 0.89$, $P = 0.05$; high pressure $\beta = -0.18$, $P = 0.17$).

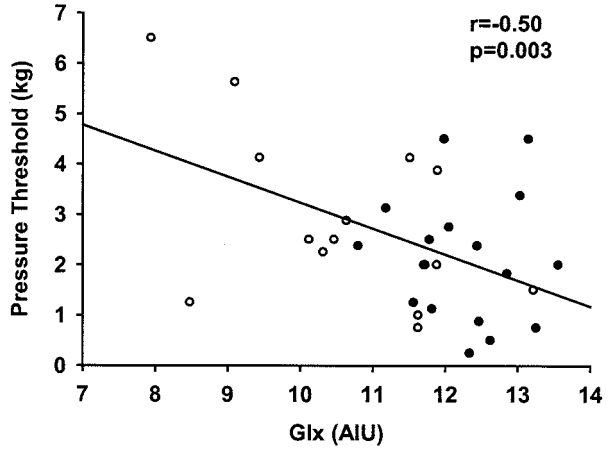


Figure 3. Glx levels within the posterior insula are negatively correlated with pressure pain thresholds. Shown is a scatterplot of Glx concentrations versus medium pressure pain thresholds for FM patients (solid circles) and healthy controls (open circles). Also shown is the regression line across groups. See Figure 2 for definitions.

Table 3. Regression results of association of posterior insular Glx and Glu levels with group and pressure threshold*

Dependent variable, predictor	β (95% CI)	Standard error	*P*
Glx level			
Group†	1.16 (0.30 to 2.03)	0.42	0.01
Pressure pain (medium)	−0.54 (−0.87 to −0.22)	0.16	0.002
Glu level			
Group†	0.75 (−0.09 to 1.59)	0.41	0.08
Pressure pain (medium)	−0.36 (−0.68 to −0.05)	0.15	0.03

* 95% CI = 95% confidence interval (see Table 1 for other definitions).
† The healthy controls group is the reference group.

Overall, these data indicate that FM patients have elevated Glu and Glx levels within the posterior insula and that these levels are associated with pressure pain thresholds. Since there was no significant group–pressure pain interaction term, the relationship between Glu and Glx levels and pain threshold was similar across groups. Although the relationship was similar, it was shifted toward higher metabolite levels for the patient group.

DISCUSSION

These findings point toward a potential role of insular Glu in the pathophysiology of FM. The levels of Glu in the posterior insula were higher for individuals with FM than for controls, and the levels of Glu were negatively correlated with pressure pain thresholds. This suggests that the "leftward shift" in the stimulus response function seen in both experimental pain testing and functional imaging in FM (i.e., hyperalgesia) is associated with higher levels of Glu in certain brain regions involved in pain processing, such as the posterior insula (9,11). The posterior insula is known to play a prominent role in pain and interoceptive sensory processing (22,23), whereas the anterior insula is involved in the affective processing of pain and other subjective feelings (22,24). Since the levels of Glu in the anterior insula did not differ between the groups, this could suggest that a component of this disorder involves an amplification in sensory, but not affective, processing.

Our findings are entirely consistent with the broader literature and knowledge regarding FM and related syndromes, which suggests that individuals with these conditions are at the far right end of the bell-shaped curve of pain and sensory processing in the population (25). Our data suggest that Glu is playing a role in this augmented pain processing in those individuals who have elevated Glu levels. Since higher Glu levels were associated with lower pain thresholds, this suggests that Glu in the posterior insula is related to pain processing. The elevated levels of Glu in the FM group could raise the set point of baseline neural activity in this region, which could result in augmented responses to painful stimuli. In a related line of inquiry, cold pain has been shown to increase Glu levels within the cingulate of pain-free controls (26).

FM patients may have more Glu within their synaptic vesicles, higher numbers or densities of glutamatergic synapses, or even less uptake of Glu from the synaptic cleft. Any of these changes would be consistent with the hypothesis that there is augmentation of pain and sensory processing in FM. If true, this aspect of the pathophysiology of FM may be more similar to conditions such as epilepsy or neurodegenerative diseases than to the rheumatic syndromes with which it has historically been associated. For example, in epilepsy, cortical and subcortical neurons appear to be hyperexcitable as a result of elevated concentrations of Glu (27). These clusters of excited neurons are thought to form a locus of heightened activity, which can then initiate a spreading wave of action potentials that propagate to other connected brain regions. FM may simply represent a condition in which glutamatergic "hyperactivity" occurs within brain regions devoted to processing and modulating pain. This could arise from local increases in Glu levels or enhanced ascending activity to this area. This hypothesis is consistent with the fact that one of the Food and Drug Administration–approved medications for FM is pregabalin, a drug whose action is thought to involve inhibition of presynaptic Glu release (28). Interestingly, this drug is also used in the treatment of epilepsy (29).

As with any trial, our study has limitations. The voxels used during H-MRS include multiple cell types. Our metabolite estimates of Glu and Glx reflect an ensemble average of all cell types (i.e., neurons, astrocytes, and glia) within the tissue samples. As such, our findings must be interpreted with the knowledge that the cellular and subcellular location of the elevated Glu is unknown. That said, our methods have been empirically validated by other reported single-voxel spectroscopy studies (30,31), indicating that this approach is "state of the art" for noninvasive assessment of molecular concentrations within the brain.

We also recognize that our findings pertain only to the insula. Future studies that detect Glu levels in other pain processing structures, such as the secondary somatosensory cortex, amygdala, cingulate, etc., are needed to determine the spatial extent of elevated Glu levels. Of note, a recent H-MRS study has shown decreased NAA levels within the hippocampus of individuals with FM (32), whereas we observed increased NAA levels in the posterior insula, although this was only a trend. In addition, our patient population excluded individuals with current major depression. It is possible that Glu levels within the anterior insula of depressed FM patients might be elevated, since it is known that the anterior insula is more involved in emotional processing of sensory information. Thus, our lack of group differences in anterior insula Glu levels may be due to the absence of depressed individuals in our sample.

Finally, although our results are significant, they originate from a relatively small number of participants. Validation of these findings in other studies could be made with larger study populations.

Overall, we find that Glu within the posterior insula is a potential pathologic factor in FM. The previously observed allodynia and hyperalgesia seen in these patients may be due to elevated excitatory glutamatergic neurotransmission within the posterior insula. Future studies are needed to determine whether these findings are observed in other functional pain syndromes.

ACKNOWLEDGMENT

We acknowledge Keith Newnham for his expertise in collecting H-MRS spectra.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Harris had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Harris, Clauw.

Acquisition of data. Harris, Kirshenbaum, Clauw.

Analysis and interpretation of data. Harris, Sundgren, Craig, Sen, Napadow, Clauw.

REFERENCES

1. Yunus MB. Towards a model of pathophysiology of fibromyalgia: aberrant central pain mechanisms with peripheral modulation. J Rheumatol 1992;19:846–50.

2. Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 1997;4:134–53.
3. Arnold LM, Pritchett YL, D'Souza DN, Kajdasz DK, Iyengar S, Wernicke JF. Duloxetine for the treatment of fibromyalgia in women: pooled results from two randomized, placebo-controlled clinical trials. J Womens Health (Larchmt) 2007;16:1145–56.
4. Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, et al, and the Pregabalin 1008-105 Study Group. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:1264–73.
5. Vitton O, Gendreau M, Gendreau J, Kranzler J, Rao SG. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. Hum Psychopharmacol 2004;19:S27–35.
6. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19–28.
7. Jacobsen S, Bredkjaer SR. The prevalence of fibromyalgia and widespread chronic musculoskeletal pain in the general population. Scand J Rheumatol 1992;21:261–3.
8. Raspe H, Baumgartner C, Wolfe F. The prevalence of fibromyalgia in a rural German community: how much difference do different criteria make? [abstract]. Arthritis Rheum 1993;36 Suppl 9:S48.
9. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46:1333–43.
10. Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH. Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol 2004;31:364–78.
11. Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH. Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. Pain 2003;105:403–13.
12. Peres MF, Zukerman E, Senne Soares CA, Alonso EO, Santos BF, Faulhaber MH. Cerebrospinal fluid glutamate levels in chronic migraine. Cephalalgia 2004;24:735–9.
13. Larson AA, Giovengo SL, Russell IJ, Michalek JE. Changes in the concentrations of amino acids in the cerebrospinal fluid that correlate with pain in patients with fibromyalgia: implications for nitric oxide pathways. Pain 2000;87:201–11.
14. Graven-Nielsen T, Aspegren KS, Henriksson KG, Bengtsson M, Sorensen J, Johnson A, et al. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. Pain 2000;85:483–91.
15. Cohen SP, Verdolin MH, Chang AS, Kurihara C, Morlando BJ, Mao J. The intravenous ketamine test predicts subsequent response to an oral dextromethorphan treatment regimen in fibromyalgia patients. J Pain 2006;7:391–8.
16. Harris RE, Sundgren PC, Pang Y, Hsu M, Petrou M, Kim SH, et al. Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia. Arthritis Rheum 2008;58:903–7.
17. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160–72.
18. Brooks JC, Nurmikko TJ, Bimson WE, Singh KD, Roberts N. fMRI of thermal pain: effects of stimulus laterality and attention. Neuroimage 2002;15:293–301.
19. Provencher SW. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magn Reson Med 1993;30: 672–9.
20. Petzke F, Gracely RH, Park KM, Ambrose K, Clauw DJ. What do tender points measure? Influence of distress on 4 measures of tenderness. J Rheumatol 2003;30:567–74.
21. Petzke F, Harris RE, Williams DA, Clauw DJ, Gracely RH. Differences in unpleasantness induced by experimental pressure between patients with fibromyalgia and controls. Eur J Pain 2005;9:325–35.
22. Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. Nat Neurosci 2000;3:184–90.
23. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 2002;3: 655–66.
24. Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. Science 2004;303:1157–62.
25. Crofford LJ, Clauw DJ. Fibromyalgia: where are we a decade after the American College of Rheumatology classification criteria were developed? [editorial]. Arthritis Rheum 2002;46:1136–8.
26. Mullins PG, Rowland LM, Jung RE, Sibbitt WL Jr. A novel technique to study the brain's response to pain: proton magnetic resonance spectroscopy. Neuroimage 2005;26:642–6.
27. Helms G, Ciumas C, Kyaga S, Savic I. Increased thalamus levels of glutamate and glutamine (Glx) in patients with idiopathic generalised epilepsy. J Neurol Neurosurg Psychiatry 2006;77:489–94.
28. Micheva KD, Taylor CP, Smith SJ. Pregabalin reduces the release of synaptic vesicles from cultured hippocampal neurons. Mol Pharmacol 2006;70:467–76.
29. Beydoun A, Nasreddine W, Atweh S. Efficacy and tolerability of pregabalin in partial epilepsy. Expert Rev Neurother 2008;8: 1013–24.
30. Hurd R, Sailasuta N, Srinivasan R, Vigneron DB, Pelletier D, Nelson SJ. Measurement of brain glutamate using TE-averaged PRESS at 3T. Magn Reson Med 2004;51:435–40.
31. Schubert F, Gallinat J, Seifert F, Rinneberg H. Glutamate concentrations in human brain using single voxel proton magnetic resonance spectroscopy at 3 Tesla. Neuroimage 2004;21:1762–71.
32. Wood PB, Ledbetter CR, Glabus MF, Broadwell LK, Patterson JC. Hippocampal metabolite abnormalities in fibromyalgia: correlation with clinical features. J Pain 2009;10:47–52.

ARTHRITIS & RHEUMATISM
Vol. 58, No. 3, March 2008, pp 903–907
DOI 10.1002/art.23223

Dynamic Levels of Glutamate Within the Insula Are Associated With Improvements in Multiple Pain Domains in Fibromyalgia

Richard E. Harris, Pia C. Sundgren, Yuxi Pang, Michael Hsu, Myria Petrou, Seong-Ho Kim, Samuel A. McLean, Richard H. Gracely, and Daniel J. Clauw

Objective. **Fibromyalgia (FM) is a chronic widespread pain condition that is thought to arise from augmentation of central neural activity. Glutamate (Glu) is an excitatory neurotransmitter that functions in pain-processing pathways. This study was carried out to investigate the relationship between changing levels of Glu within the insula and changes in multiple pain domains in patients with FM.**

Methods. **Ten patients with FM underwent 2 sessions of proton magnetic resonance spectroscopy (H-MRS) and 2 sessions of functional magnetic resonance imaging (FMRI), each conducted before and after a nonpharmacologic intervention to reduce pain. During H-MRS, the anterior and posterior insular regions were examined separately using single-voxel spectroscopy. The levels of Glu and other metabolites were estimated relative to levels of creatine (Cr) (e.g., the Glu/Cr ratio). During FMRI, painful pressures were applied to the thumbnail to elicit neuronal activation. Experimental pressure-evoked pain thresholds and clinical pain ratings (on the Short Form of the McGill Pain Questionnaire [SF-MPQ]) were also assessed prior to each imaging session**

Results. **Both experimental pain ($P = 0.047$ versus pretreatment) and SF-MPQ–rated clinical pain ($P = 0.043$ versus pretreatment) were reduced following treatment. Changes from pre- to posttreatment in Glu/Cr were negatively correlated with changes in experimental pain thresholds ($r = -0.95$, $P < 0.001$) and positively correlated with changes in clinical pain ($r = 0.85$, $P = 0.002$). Changes in the FMRI-determined blood oxygenation level–dependent effect (a measure of neural activation) were positively correlated with changes in Glu/Cr within the contralateral insula ($r = 0.81$, $P = 0.002$).**

Conclusion. **Changes in Glu levels within the insula are associated with changes in multiple pain domains in patients with FM. Thus, H-MRS data may serve as a useful biomarker and surrogate end point for clinical trials of FM.**

Fibromyalgia (FM) is a chronic widespread pain disorder that affects ~2–4% of individuals in industrialized countries (1). Although the underlying etiology of this condition is unknown, dysfunction within the central nervous system has been implicated. Results from functional magnetic resonance imaging (FMRI) (2,3), single-photon emission tomography (4), and positron emission tomography (5) support this hypothesis.

One structure that is consistently found to be associated with augmented evoked pain activity in FM is the insula (2,3). In addition to its function in speech, taste, and auditory systems, the insula is also intimately involved in somatosensory and visceral pain processing (6). It is strategically located in a bidirectional pathway between the secondary somatosensory cortex and the amygdala (6). This anatomic position may give the insula

ClinicalTrials.gov identifier: NCT00142597.

Supported by US Department of Army grant DAMD-17/002-0018 and DAMD award W81XW94-07-2-0050, and NIH/National Center for Research Resources grant M01-RR-000042. Dr. Harris' work was supported by NIH/National Center for Complementary and Alternative Medicine grant K01-AT-01111-01. Dr. McLean's work was supported by NIH grant K12-RR-017607-01.

Richard E. Harris, PhD, Pia C. Sundgren, MD, PhD, Yuxi Pang, PhD, Michael Hsu, MD, Myria Petrou, MD, Seong-Ho Kim, MD, Samuel A. McLean, MD, Richard H. Gracely, PhD, Daniel J. Clauw, MD: University of Michigan, Ann Arbor.

Dr. Harris has received consulting fees from Pfizer as part of an investigator-initiated study of acupuncture in fibromyalgia and has received speaking fees (less than $10,000) from the University of North Carolina Pelvic Pain Conference. Dr. Clauw has received consulting fees, speaking fees, and/or honoraria (less than $10,000) from Wyeth and (more than $10,000 each) from Eli Lilly, Pfizer, Cypress Bioscience, and Forest Laboratories.

Address correspondence and reprint requests to Richard E. Harris, PhD, University of Michigan, Chronic Pain and Fatigue Research Center, 24 Frank Lloyd Wright Drive, PO Box 385, Lobby M, Ann Arbor, MI 48106. E-mail: reharris@med.umich.edu.

Submitted for publication August 17, 2007; accepted in revised form November 14, 2007.

a unique regulatory function within the "pain matrix." Topographically, the posterior insula is thought to be involved in discriminative activities of sensory pain (7), whereas the anterior insula may play a greater role in processing the affective dimension of pain (8).

Glutamate (Glu) is a major excitatory neurotransmitter within the nervous system and is known to function in pain neuropathways. The binding of Glu to ionotropic receptors increases the sodium permeability of neuronal membranes and results in cell activation (i.e., membrane depolarization). Since elevated Glu levels have been reported in the cerebrospinal fluid of patients with FM (9), it is reasonable to suspect that this molecule may be responsible for the augmented pain transmission observed in FM (2,3).

We performed a longitudinal proton magnetic resonance spectroscopy (H-MRS) study to investigate the role of Glu within the insula of patients with FM. H-MRS is a noninvasive procedure that can be used to determine the relative concentration of specific brain metabolites in vivo. We focused our investigation on the changing levels of Glu following a nonpharmacologic treatment, within both the anterior and posterior insula of patients with FM. We hypothesized that changes in the levels of Glu should be positively correlated with changes in clinical pain. Conversely, changes in Glu levels should be negatively correlated with changes in pressure-evoked pain thresholds, since lower thresholds are indicative of greater pain sensitivity. In addition, we used FMRI in these same subjects to determine whether changes in Glu levels were related to changes in pain-related neural activity.

PATIENTS AND METHODS

Participants. As part of an ongoing study investigating the impact of acupuncture treatment in FM, 10 female patients (mean ± SD age 48 ± 15 years) were examined in 2 sessions of H-MRS and 2 sessions of FMRI, with the sessions spaced 1 month apart (Figure 1). Participants were randomized to receive either 9 traditional acupuncture treatments or 9 non–skin-penetrating sham acupuncture treatments, administered between imaging sessions. All analyses described herein were carried out in a blinded manner with the treatment assignment masked, since we were not interested in the potential differential effects between treatment with acupuncture and sham treatment, but rather in whether changes in the levels of Glu correspond to changes in pain. All participants gave their written informed consent, and all study protocols were approved by the University of Michigan Institutional Review Board.

Participant inclusion and exclusion criteria have been reported previously (5). All participants met the American College of Rheumatology 1990 criteria for the diagnosis of FM (10) and had a disease duration of at least 1 year. In addition, all patients reported experiencing pain for more than 50% of the days prior to the trial period.

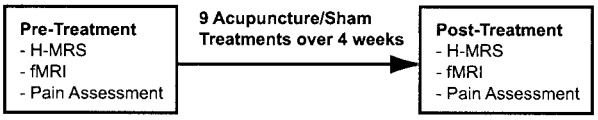


Figure 1. Experimental design. Patients with fibromyalgia underwent pretreatment assessments with both proton magnetic resonance spectroscopy (H-MRS) and functional magnetic resonance imaging (FMRI). During H-MRS testing, resting levels of glutamate were obtained in the insula. During FMRI, neural activations (i.e., BOLD [blood oxygenation level–dependent] effects) were elicited with painful pressure stimuli applied to the left thumbnail bed. Pretreatment assessments of clinical pain using the Short Form of the McGill Pain Questionnaire, and experimental pressure-evoked pain sensitivity thresholds were also obtained. Following the baseline assessment, participants received either 9 acupuncture treatments or 9 sham acupuncture treatments over 4 weeks. H-MRS, FMRI, and pain outcomes were then measured again, following the last treatment.

H-MRS. All participants underwent conventional MR imaging of the brain on a General Electric 3.0T MR scanner (GE, Milwaukee, WI). Single-voxel spectroscopy (SVS) was performed using point-resolved spectroscopy, with a repetition time (TR) of 3,000 msec, echo time (TE) of 30 msec, 90° flip angle, number of excitations 8, field of view (FOV) 16 cm, and volume of interest (VOI) of $2 \times 2 \times 3$ cm. During each session, 2 separate SVS sequences were performed, once with the VOI placed in the right anterior insula and once in the right posterior insula (Figure 2A). The right insula was chosen because it is contralateral to the pressure-evoked pain stimulus applied during FMRI. Patients were at rest during both H-MRS sessions.

The raw data from each SVS sequence were subjected to manual postprocessing using H-MRS software (LCModel; Oakville, Ontario, Canada) (Figure 2B). Values for Glu, glutamine (Gln), and the combination of Glu and Gln (Glx) were calculated as ratios to an internal standard, the creatine (Cr) level (e.g., Glu/Cr). Similar calculations were done for other major metabolites, including *N*-acetylaspartate (NAA), choline (Cho) compounds, and myoinositol (MI). Although these other metabolites are not known to play a role in neuronal activity, they were measured to assess the relative specificity of Glu and Gln in our analyses.

Functional MRI. To assess the relationship between changes in Glu and changes in neural activity, all participants also underwent 2 FMRI sessions, once prior to treatment and once posttreatment. Functional MRI scans were acquired on the same 3.0T scanner as used for H-MRS. On each scanning day, subjects completed 2 FMRI runs, acquired with a spiral gradient-echo sequence (TR 2,500 msec, TE 30 msec, 90° flip angle, FOV 22 cm). Slices were 3-mm thick, with an in-plane resolution of 3.125×3.125, acquired at 48 locations parallel to the anterior-posterior commissure plane. Preprocessing was performed using statistical parametric mapping 2 (SPM2; Wellcome Department of Cognitive Neurology, London, UK) and included correction for slice-acquisition time to the middle slice, realignment to the first volume of each run to correct for

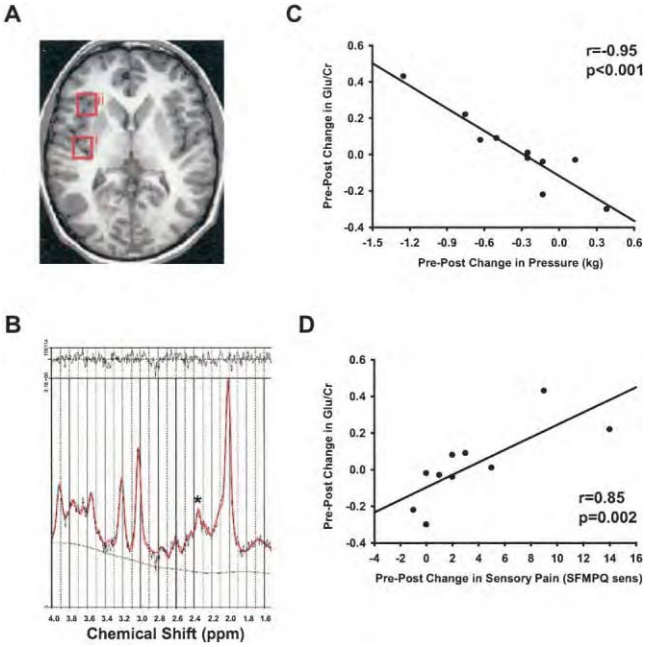


Figure 2. Association of changing levels of glutamate (Glu) with improvements in pain outcomes in patients with fibromyalgia (FM). **A,** Axial T1-weighted image showing single-voxel placement for both the posterior (i) and anterior (ii) right insula in proton magnetic resonance spectroscopy (H-MRS). **B,** Representative H-MRS spectrum from the posterior insula of a patient with FM, analyzed by fitting data with the LCModel, which uses a linear combination of individual spectra obtained from pure molecular species to fit the experimental spectra (red trace); $*$ = resonance from 2 Glu γ-proton resonances at 2.35 ppm. Values for Glu were calculated as a ratio to the creatine (Cr) internal standard (Glu/Cr). **C,** Negative correlation of pre- to posttreatment changes in Glu/Cr within the posterior insula with pre- to posttreatment changes in mildly painful pressure–evoked pain thresholds. **D,** Positive correlation of pre- to posttreatment changes in Glu/Cr within the posterior insula with pre- to posttreatment changes in clinical pain (assessed as the sensory pain score on the Short Form of the McGill Pain Questionnaire [SF-MPQ]).

intrascan movement, and smoothing with a Gaussian kernel of 8 mm full width at half maximum to compensate for small residual anatomic variations across subjects. Smoothed images were then band pass–filtered to eliminate low-frequency signals.

A general linear model was constructed with parameters corresponding to the type of pressure stimulus applied (either no touch or innocuous touch) in each block, with Gracely Box Scale (GBS) scores of 0.5 for low pain,7.5 for mild pain, and 13.5 for moderate pain; modeling of each run was carried out separately. Blocks were 25 seconds in duration and presented according to a fixed pseudorandom paradigm in which every other block consisted of the "no touch" condition. To allow for comparison across individuals, 1 of the 3 painful pressure blocks was set to 2 kg/cm^2. Each stimulus block was convolved with a canonical hemodynamic response function. Parameter estimates of block-related activity were established for each voxel, and contrast images were calculated by applying a linear contrast of the parameter estimates of the 2 kg/cm^2 pressure versus the "no touch" condition for each participant. The resulting statistical images obtained for each subject were then spatially normalized into International Consortium for Brain Mapping space by applying T1-weighted spoiled gradient echo transformation parameters to the SPM2 contrast image.

Differences in the blood oxygenation level–dependent (BOLD) effects (a measure of neural activation) from pretreatment to posttreatment were calculated (as a percentage) for the entire volume in each individual, and were assessed for correlations with Glu/Cr change scores (pretreatment to posttreatment) in the posterior insula. Our a priori hypothesis was that changes in BOLD activation within the insula would be correlated with changes in Glu/Cr values. Therefore, we used an uncorrected significance threshold of $P < 0.001$, with a minimum cluster size of 10 voxels for clusters identified within the insula. Individual BOLD activation responses were extracted using the Marsbar Region of Interest Toolbox (version 0.38; http://marsbar.sourceforge.net).

Clinical pain. Assessment of clinical pain was performed prior to each imaging session using ratings on the Short Form of the McGill Pain Questionnaire (SF-MPQ) (11). Our analysis focused on the sensory dimension of pain assessed by this questionnaire, since the magnitude of sensory pain was reduced with treatment.

Experimental pain. Pressure-evoked pain tenderness was assessed prior to each imaging session (12,13). Briefly, discrete pressure stimuli were applied to the subject's left thumbnail using a stimulation device that eliminates any direct examiner–subject interaction. Pain intensity ratings were recorded on a GBS questionnaire using a random presentation paradigm. During the testing, stimulus pressures were determined interactively; a computer program continuously adjusted the stimulus pressures at 3 levels to produce the same response distribution (i.e., GBS scores of 0.5, 7.5, and 13.5) in each subject. We assessed correlations of changes in metabolite levels with changes in the pressure-evoked pain thresholds at the mildly painful pressure level (GBS score of 7.5), since this threshold increased following treatment.

Statistical analysis. Ratios of the different metabolites to Cr, percent changes in BOLD activation, and pain ratings were analyzed using SPSS version 14 (SPSS, Chicago, IL). Due to our small sample size, we performed nonparametric Spearman's correlation tests to determine significant relationships between Glu/Cr and changes in pain outcomes. For these correlation analyses, a Bonferroni-corrected P value of less than 0.0042 (calculated as 0.05 divided by 12) was applied as the level of significance for correlations between changes in metabolite ratios (Glu/Cr, Gln/Cr, and Glx/Cr) and changes in pain domains (i.e., 2 brain regions [anterior and posterior insula], 2 pain domains [clinical and experimental], and 3 metabolites). A similar correction (corrected $P < 0.0042$) was performed for the analysis of baseline and posttreatment metabolite ratios within the posterior insula and changes in pain (i.e., 3 metabolites, 2 time points, and 2 pain domains). Nonparametric Wilcoxon's signed rank tests were performed to determine changes from pretreatment to posttreatment in clinical and experimental evoked pain.

RESULTS

Following acupuncture or sham treatments in this population of patients with FM, the pressure-evoked pain sensitivity after application of mildly painful pressures was significantly reduced (mean difference in experimental pain thresholds −0.34 kg [SD 0.46 kg]; $P = 0.047$). Moreover, clinical pain improved from pre- to posttreatment according to SF-MPQ ratings of the sensory dimension of pain (mean difference in clinical pain ratings 3.50 [SD 4.70]; $P = 0.043$).

Figure 2B depicts a representative spectrum obtained from the posterior insula of a patient prior to treatment. A significant negative correlation was detected between change scores for Glu/Cr in the posterior insula from pre- to posttreatment and changes in the pressures required to elicit mild pain from pre- to posttreatment ($r = -0.95$, $P < 0.001$) (Figure 2C). Similarly, a positive correlation was detected between changes in Glu/Cr in the posterior insula and changes in SF-MPQ (sensory) clinical pain ratings ($r = 0.85$, $P = 0.002$) (Figure 2D). Furthermore, higher levels of Gln/Cr in the posterior insula were also associated with greater reductions in clinical pain posttreatment ($r = 0.81$, $P = 0.004$).

No significant correlations were detected between change scores of any other metabolite ratios (i.e., NAA/Cr, Cho/Cr, or MI/Cr) in the posterior insula and changes in either clinical pain ratings or experimental evoked pain thresholds (all $P > 0.10$). In addition, no significant changes in Cr concentrations were detected within the posterior insula ($P = 0.98$).

Since there is debate as to whether H-MRS can accurately measure Glu separately from Gln within humans at 3T, we also assessed the combination of Glu and Gln as a ratio (i.e., Glx/Cr). Changes in Glx/Cr within the anterior insula ($r = -0.63$, $P = 0.049$) and posterior insula ($r = -0.62$, $P = 0.058$) were both negatively correlated with changes in pressure-evoked pain, albeit at the level of trend toward significance. Overall, these data are consistent with the idea that either insular Glu or insular Gln or both are associated with changes in multiple pain domains in FM.

Since Glu functions in pain neurotransmission, we next investigated whether pre- to posttreatment changes in Glu/Cr within the right posterior insula were associated with changes in the BOLD responses elicited by painful pressure applied to the thumbnail bed. Changes in Glu/Cr within the right posterior insula were positively correlated with changes in BOLD activation within the left posterior insula (T score 6.6, uncorrected $P < 0.001$; Montreal Neurological Institute (MNI) coordinates $x = -42$, $y = -12$, $z = 0$) (Figure 3A). In contrast, a negative correlation, at the level of trend toward significance, was detected for changes in Glu/Cr and changes in BOLD activation in the right posterior insula (T score 4.1, uncorrected $P = 0.0018$; MNI coordinates $x = 38$, $y = -14$, $z = -6$) (Figure 3B).

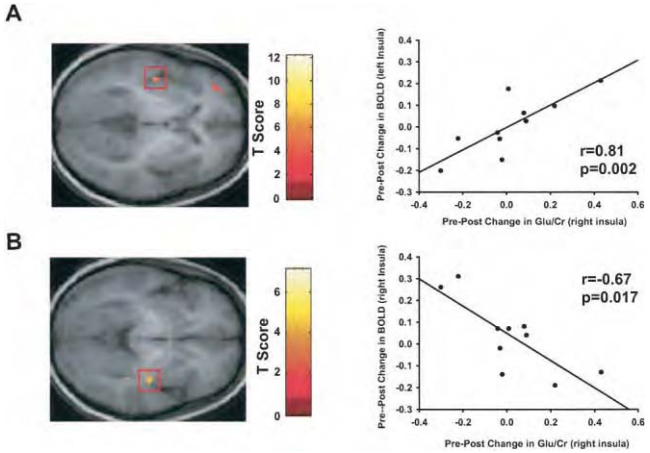


Figure 3. Association of dynamic levels of glutamate:creatine (Glu/Cr) within the posterior insula with changes in neural activity. **A,** Positive correlation of pre- to posttreatment changes in functional magnetic resonance imaging (FMRI)–determined blood oxygenation level–dependent (BOLD) activation within the left posterior insula with pre- to posttreatment changes in Glu/Cr within the right posterior insula (left). Scatterplot (right) depicts individual BOLD and Glu/Cr changes. **B,** Negative correlation of pre- to posttreatment changes in FMRI-determined BOLD activation within the right posterior insula with pre- to posttreatment changes in Glu/Cr within the right posterior insula (left). Scatterplot (right) depicts individual BOLD and Glu/Cr changes.

DISCUSSION

These data are the first evidence of a correlation between changing levels of insular Glu and changes in pain in patients with FM. Since Glu is a major excitatory neurotransmitter involved in pain transmission, these observations are not unexpected. Our data are also consistent with findings from a recent H-MRS study in which increases in Glu/Cr within the anterior cingulate were observed in response to cold pain in healthy pain-free controls (14). However, the present data show primarily the converse of this relationship, namely, reductions in pain in association with lower Glu/Cr values.

Since detecting Glu-specific concentrations accurately at 3T in humans is difficult because of the

overlapping proton resonances between Gln and Glu, we also investigated the combinations of Glu/Cr and Gln/Cr (i.e., Glx/Cr), which may be less controversial (14). Similar to the above-described results, we found that pre- to posttreatment changes in Glx/Cr within the insula were negatively correlated with pre- to posttreatment changes in pressure-evoked pain thresholds. Since we did not detect a significant relationship between changes in any other major metabolites and improvements in pain outcomes, our findings are likely to be specific for Glu and/or Gln.

It is unlikely that our Glu measurements reflect solely synaptic levels of this neurotransmitter, since the volume of brain tissue sampled also included cell bodies and processes of nonneuronal cells. Our measurements probably reflect an average of combined intra- and extracellular Glu levels arising from both neuronal and nonneuronal cells. A growing body of research over the last decade suggests that the Glu–Gln cycle between astrocytes and neurons may regulate synaptic activity (15). Interestingly, individuals with the greatest pain reduction also showed higher levels of Gln/Cr posttreatment, suggesting that our treatment intervention may have altered the Glu–Gln cycle.

Consistent with our observed changes in Glu functioning in evoked pain activity, we also detected changes in FMRI-determined BOLD activation that occurred in parallel to the dynamic Glu/Cr levels in the posterior insula. These data are consistent with the idea that neural activity is augmented within this region in FM (2,3). However, we found a differential relationship between Glu/Cr within the right posterior insula and changes in BOLD activity within the left insula compared with the right insula. This observation was unexpected, and may reflect the possibility that our intervention influenced the left and right insula in a differential manner. Alternatively, Glu levels may influence activation of the BOLD effect differentially during task conditions compared with resting conditions. Additional research will be required to further explore this finding.

Due to the small sample size used in our trial, these findings should be interpreted carefully. However, our data suggest that Glu may be a useful biomarker for disease severity in FM. Thus, future investigations of Glu within FM patient populations are warranted.

ACKNOWLEDGMENT

We acknowledge Keith Newnham for his expertise in collecting the H-MRS spectrum data.

AUTHOR CONTRIBUTIONS

Dr. Harris had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Harris, Sundgren, Petrou, Gracely, Clauw.
Acquisition of data. Harris, Sundgren.
Analysis and interpretation of data. Harris, Pang, Hsu, Kim, McLean, Gracely, Clauw.
Manuscript preparation. Harris, Sundgren, Petrou, McLean, Gracely, Clauw.
Statistical analysis. Harris.

REFERENCES

1. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19–28.
2. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46:1333–43.
3. Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH. Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol 2004;31:364–78.
4. Mountz JM, Bradley LA, Alarcon GS. Abnormal functional activity of the central nervous system in fibromyalgia syndrome. Am J Med Sci 1998;315:385–96.
5. Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK. Decreased central μ-opioid receptor (MOR) availability in fibromyalgia (FM). J Neurosci 2007;27:10000–6.
6. Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res Brain Res Rev 1996;22: 229–44.
7. Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. Nat Neurosci 2000;3:184–90.
8. Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. Science 2004;303:1157–62.
9. Sarchielli P, Mancini ML, Floridi A, Coppola F, Rossi C, Nardi K, et al. Increased levels of neurotrophins are not specific for chronic migraine: evidence from primary fibromyalgia syndrome. J Pain 2007;8:737–45.
10. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. Arthritis Rheum 1990;33:160–72.
11. Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30:191–7.
12. Petzke F, Gracely RH, Park KM, Ambrose K, Clauw DJ. What do tender points measure? Influence of distress on 4 measures of tenderness. J Rheumatol 2003;30:567–74.
13. Petzke F, Harris RE, Williams DA, Clauw DJ, Gracely RH. Differences in unpleasantness induced by experimental pressure between patients with fibromyalgia and controls. Eur J Pain 2005;9:325–35.
14. Mullins PG, Rowland LM, Jung RE, Sibbitt WL Jr. A novel technique to study the brain's response to pain: proton magnetic resonance spectroscopy. Neuroimage 2005;26:642–6.
15. Hertz L, Zielke HR. Astrocytic control of glutamatergic activity: astrocytes as stars of the show. Trends Neurosci 2004;27:735–43.

NeuroImage 47 (2009) 1077–1085

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Traditional Chinese acupuncture and placebo (sham) acupuncture are differentiated by their effects on μ-opioid receptors (MORs)

Richard E. Harris [a,*], Jon-Kar Zubieta [b,c], David J. Scott [d], Vitaly Napadow [e], Richard H. Gracely [f], Daniel J. Clauw [a]

[a] Department of Anesthesiology, University of Michigan, Ann Arbor, MI 48109, USA
[b] Department of Psychiatry and Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI 48109, USA
[c] Department of Radiology, University of Michigan, Ann Arbor, MI 48109, USA
[d] Omneuron Incorporated, Menlo Park, CA 94025, USA
[e] MGH/MIT/HMS Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Charlestown, MA 02129, USA
[f] Department of Internal Medicine, University of Michigan, Ann Arbor, MI 48109, USA

ARTICLE INFO

Article history:
Received 22 December 2008
Revised 10 April 2009
Accepted 23 May 2009
Available online 6 June 2009

Keywords:
Acupuncture
Opioid
Mu
Fibromyalgia
Pain
Positron emission tomography

ABSTRACT

Controversy remains regarding the mechanisms of acupuncture analgesia. A prevailing theory, largely unproven in humans, is that it involves the activation of endogenous opioid antinociceptive systems and μ-opioid receptors (MORs). This is also a neurotransmitter system that mediates the effects of placebo-induced analgesia. This overlap in potential mechanisms may explain the lack of differentiation between traditional acupuncture and either non-traditional or sham acupuncture in multiple controlled clinical trials. We compared both short- and long-term effects of traditional Chinese acupuncture (TA) versus sham acupuncture (SA) treatment on *in vivo* MOR binding availability in chronic pain patients diagnosed with fibromyalgia (FM). Patients were randomized to receive either TA or SA treatment over the course of 4 weeks. Positron emission tomography (PET) with ^{11}C-carfentanil was performed once during the first treatment session and then repeated a month later following the eighth treatment. Acupuncture therapy evoked short-term increases in MOR binding potential, in multiple pain and sensory processing regions including the cingulate (dorsal and subgenual), insula, caudate, thalamus, and amygdala. Acupuncture therapy also evoked long-term increases in MOR binding potential in some of the same structures including the cingulate (dorsal and perigenual), caudate, and amygdala. These short- and long-term effects were absent in the sham group where small reductions were observed, an effect more consistent with previous placebo PET studies. Long-term increases in MOR BP following TA were also associated with greater reductions in clinical pain. These findings suggest that divergent MOR processes may mediate clinically relevant analgesic effects for acupuncture and sham acupuncture.

Introduction

Acupuncture as a component of East-Asian medical systems has been used to treat pain for over two millennia however the cellular and molecular constituents of this therapy remain largely unknown. Prevailing theories, arising largely from studies in animals, suggest that endogenous opioids and their associated receptors are involved in this treatment (He et al., 1985; Pert et al., 1981; Ho and Wen, 1989; Pomeranz and Chiu, 1976; Chen et al., 1996). Most studies have focused on the opioid neurotransmitters (Stux and Hammerschlag, 2001), where enhanced release seems to accompany needle insertion, however less attention has been paid to the opioid receptors themselves (e.g. the μ, κ, and δ opioid receptor classes) and their relationship with clinical response.

Recent controversy in the field of acupuncture research was generated when several large scale randomized controlled trials in chronic pain patients failed to show superiority of acupuncture over sham acupuncture methods (Brinkhaus et al., 2006; Linde et al., 2005; Melchart et al., 2005; Harris et al., 2005). This has lead opponents of acupuncture therapy to suggest that it is no more effective than a placebo intervention. Since placebo administration also induces activation of opioid receptors, specifically the μ-opioid receptor (MOR) class (Benedetti and Amanzio, 1997; Zubieta et al., 2005; Amanzio and Benedetti, 1999; Levine et al., 1978; Pomeranz and Chiu, 1976), acupuncture may indeed operate in part via placebo mechanisms.

Neuroimaging methods allow for the ability to explore the central neurobiological mechanisms of both acupuncture and placebo interventions. Recent functional magnetic resonance imaging (fMRI)

* Corresponding author. Chronic Pain and Fatigue Research Center, 24 Frank Lloyd Wright Drive, PO Box 385, Lobby M, Ann Arbor, MI 48106, USA. Fax: +1 734 998 6900.
E-mail address: reharris@med.umich.edu (R.E. Harris).

1053-8119/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2009.05.083

studies demonstrate deactivation of limbic structures including the amygdala, the hippocampus, and the perigenual cingulate via a mechanism that is distinct from pain and sham stimulation (Hui et al., 2000, 2005; Napadow et al., 2007). Thus while traditional acupuncture and sham acupuncture may have equivalent analgesic effects they may differ significantly in their underlying neurobiological response.

Here we directly explore the involvement of the endogenous opioid system during acupuncture treatment of chronic pain patients diagnosed with fibromyalgia (FM) (Wolfe et al., 1995). FM is a relatively common chronic pain condition thought to originate from augmented pain processing in the central nervous system (Gracely et al., 2002). We have previously demonstrated that FM patients have reduced central μ-opioid receptor (MOR) binding potential (BP; an *in vivo* measure of binding availability) using ^{11}C-carfentanil (CFN) positron emission tomography (PET) with the μ-opioid selective radiotracer [^{11}C]carfentanil (Harris et al., 2007). In that study patients with greater clinical pain displayed reduced MOR BP. Here we perform CFN PET on FM patients before and following acupuncture and sham treatment. We reasoned that dynamics in receptor binding could complement previous acupuncture research which has focused largely on the release of endogenous opioids. One study has examined acupuncture effects on central opioid receptor binding, however that study used a non-selective opioid receptor agonist and did not examine effects within a clinical population (Dougherty et al., 2008).

Based on animal data and *in vitro* measures of MOR binding (Gao et al., 1997), it was hypothesized that long-term acupuncture therapy may result in increased MOR BP, or receptor availability *in vivo*. Further, we reasoned that these effects would not be observed in the sham treatment group, thus differentiating "placebo" from active treatment conditions. Finally, since regional decreases in MOR BP have been associated with greater clinical pain in FM patients (Harris et al., 2007), increases in BP were expected to be associated with reduced clinical pain.

Materials and methods

Participants

As part of a study investigating the impact of acupuncture treatment in FM, 20 female patients (mean (SD) age:44.3 (13.6) yrs) were examined with two CFN PET imaging sessions. Participants were randomized to receive either nine traditional acupuncture (TA; $n=10$) or nine non-skin penetrating sham acupuncture (SA; $n=10$) treatments. Demographics of the sample population are presented in Supplementary Table 1. No significant differences were detected between participants in the TA and SA groups for either age, race, duration of FM symptoms, or pre-treatment clinical pain scores. Participants gave written informed consent and all study protocols were approved by the University of Michigan Institutional Review Board and the Radioactive Drug Research Committee.

All participants: 1) met the American College of Rheumatology (1990) criteria (Wolfe et al., 1990) for the diagnosis of FM for at least 1 year; 2) had continued presence of pain more than 50% of days; 3) were willing to limit the introduction of any new medications or treatment modalities for control of FM symptoms during the study; 4) were over 18 and under 75 years of age; 5) were female; 6) were right handed; 7) had no alcohol intake 48 h prior to PET studies; and 8) were capable giving written informed consent. Participants were excluded if they: 1) had previous experience with acupuncture; 2) had current use or a history of use of opioid or narcotic analgesics; 3) had a history of substance abuse; 4) had the presence of a known coagulation abnormality, thrombocytopenia, or bleeding diathesis that may preclude the safe use of acupuncture; 5) had the presence of concurrent autoimmune or inflammatory disease such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, etc. that causes pain; 6) had concurrent participation in other therapeutic trials; 7) were pregnant and nursing mothers; 8) had severe psychiatric illnesses (current schizophrenia, major depression with suicidal ideation, substance abuse within 2 years); 9) had current major depression; or 10) had contraindications to PET. Concomitant medications are listed in Supplementary Table 2.

Positron emission tomography (PET)

Image acquisition

Scans were acquired with a Siemens (Knoxville, TN) HR$^+$ scanner in 3-D mode (reconstructed FWHM resolution ~5.5 mm in-plane and 5.0 mm axially), with septa retracted and scatter correction. Participants were positioned in the PET scanner gantry, and an intravenous (antecubital) line was placed in the right arm. A light forehead restraint was used to eliminate intrascan head movement. CFN was synthesized at high specific activity (>2000 Ci/mmol), as previously described (Jewett, 2001); 10–15 mCi (370–555 MBq) were administered during the scan. Fifty percent of the CFN dose was administered as a bolus, and the remaining 50% by continuous infusion for the remainder of the study. Twenty-eight frames of images were acquired over 90 min with an increasing duration (30 s up to 10 min). The total mass of carfentanil administered was maintained below 0.03 μg/kg, ensuring that the compound was administered in a tracer quantity (i.e. a sub-pharmacological dose). Receptor occupancy by this mass of carfentanil is estimated to be 0.2% to 0.6% depending on the brain region (Gross-Isseroff et al., 1990; Gabilondo et al., 1995). The methodology employed to quantify MOR sites (i.e., bolus–continuous infusion to more rapidly achieve full equilibrium conditions across kinetic compartments) has been shown not to be significantly susceptible to changes in blood flow, and therefore tracer transport, that could be caused by procedures such as acupuncture (Zubieta et al., 2003b; Joshi et al., 2008).

Fig. 1a displays the timeline for PET image acquisition, treatment procedures, and study outcomes. For the first and second PET image session, PET1 and PET2 respectively, we used data from minutes 10 to 40 as our baseline measurement because the slope of the Logan plot (see below) for CFN becomes linear at approximately 7.5 min following CFN infusion (Zubieta et al., 2003b). This was followed by TA and SA procedures (see below) performed between minutes 40 to 45. Data from minutes 40 to 45 were omitted due to head motion during treatment procedures. After needle insertion and manipulation, scans from 45 to 90 min during PET1 were used as the short-term treatment measurement (i.e. treatment1). During minutes 45 to 90, needles were retained in the TA group, whereas no needles were present in the SA group since SA did not involve skin penetration. For analysis of long-term changes in MOR binding, changes between PET1 and PET2 baseline scans, baseline1 and baseline2 respectively, were examined.

Anatomical MRI scans were acquired in all subjects on a 3 T scanner (Signa LX, General Electric, Milwaukee, WI). The acquisition sequence was axial SPGR Inverse Recovery-Prepared MR [echo time (TE) = 3.4 ms, repetition time (TR) = 10.5 ms, inversion time (TI) = 200 ms, flip angle = 25°, number of excitations (NEX) = 1, using 124 contiguous images, 1.5 mm-thickness].

Image processing

Images were reconstructed using iterative algorithms (brain mode; FORE/OSEM 4 iterations, 16 subsets; no smoothing) into a 128 × 128 pixel matrix in a 28.8 cm diameter field of view. Attenuation correction was performed through a 6-min transmission scan (^{68}Ge source) obtained prior to each PET study, also with iterative reconstruction of the blank/transmission data followed by segmentation of the attenuation image. Small head motions during emission scans were corrected by an automated computer algorithm for each subject before analysis, and the images were co-registered to each other with the same software (Minoshima et al., 1993). Time points

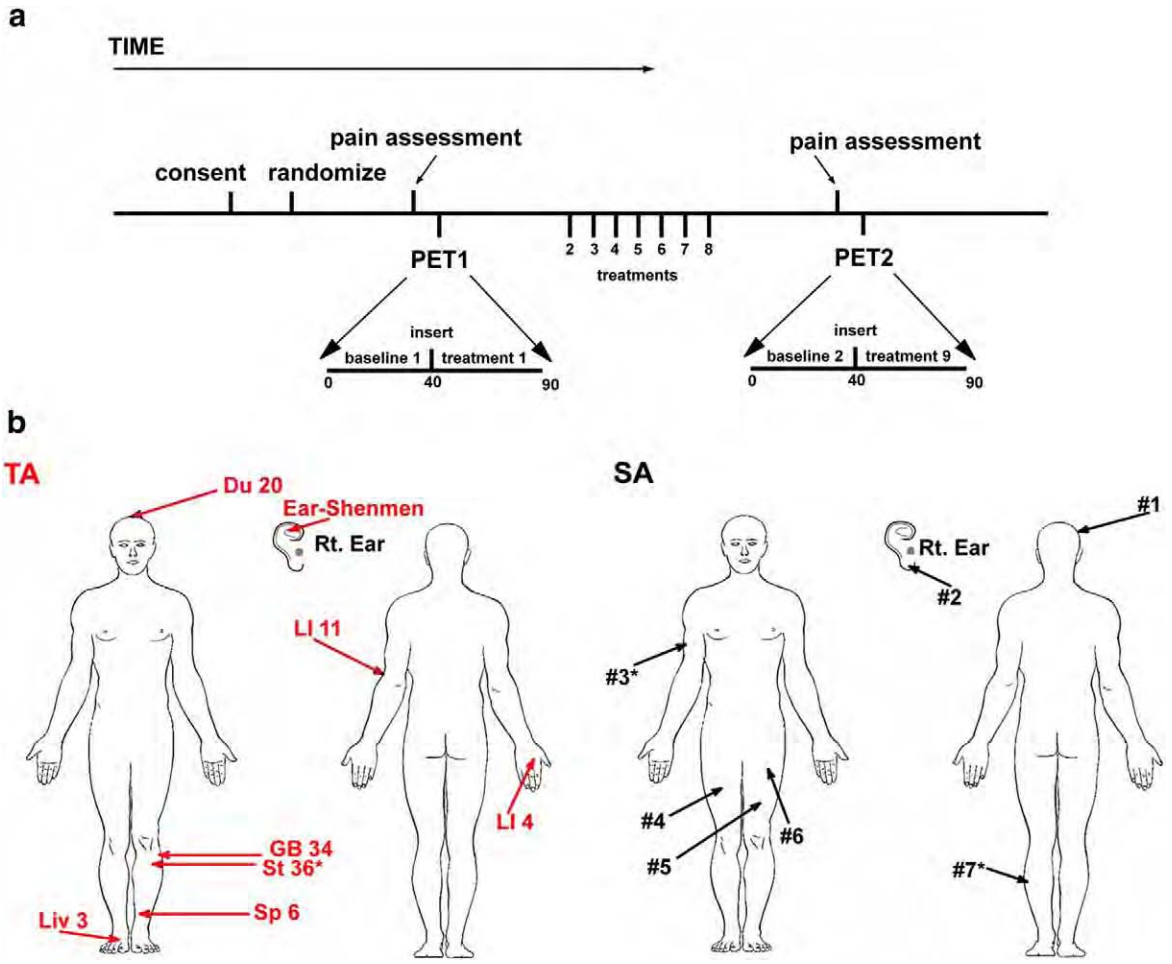


Fig. 1. Study design. (a) Participant timeline from consent, through PET imaging sessions, and treatments. Following consent, all participants were randomized to either the traditional acupuncture (TA) or sham acupuncture (SA) treatment groups. Immediately before both PET imaging sessions (i.e. PET1 and PET2), participants completed the SF MPQ to assess clinical pain. During PET1, participants underwent a baseline scan (baseline1) and a treatment scan (treatment1) both of which were used to estimate short-term effects on MOR binding. Participants then received seven acupuncture or sham treatments outside of the scanner. This was followed by PET2, a second imaging session. The baseline scan during PET2 was used for comparison with the baseline scan in PET1 to estimate long-term changes in resting MOR binding. (b) TA (red) and SA (black) point locations. Similar body regions were used for both interventions.

were then decay-corrected during reconstruction of the PET data. Image data were then transformed on a voxel-by-voxel basis into two sets of parametric maps: (a) a tracer transport measure (K_1 ratio), and (b) a receptor-related measure (DVR). To avoid the need for arterial blood sampling, the tracer transport and binding measures were calculated using a modified Logan graphical analysis (Logan et al., 1996), using the occipital cortex (an area devoid of MORs) as the reference region. The slope of the Logan plot was used for the estimation of the distribution volume ratio (DVR), a measure equal to the $f_2(B_{max}/K_d)+1$ for this receptor site and radiotracer. B_{max}/K_d (or DVR-1) is the receptor-related measure or binding potential (BP). The term f_2 refers to the concentration of free radiotracer in the extracellular fluid and is considered to represent a constant and very small value. K_1 and DVR images for each experimental period and MR images were co-registered to each other and to the International Consortium for Brain Mapping (ICBM) stereotactic atlas orientation. The accuracy of coregistration and non-linear warping algorithms was confirmed for each subject individually by comparing the transformed MRI and PET images to each other and the ICBM atlas template.

Group differences were mapped into stereotactic space using t maps of statistical significance with SPM99 (Wellcome Department of Cognitive Neurology, London, UK) and Matlabv6.5 (MathWorks, Natick MA) software, with a general linear model. No global normalization was applied to the data, and therefore the calculations presented are based on absolute B_{max}/K_d estimates. Only regions with specific MOR BP were included in the analyses (i.e. voxels with DVR values>1.1, or BP>0.1). To compensate for small residual anatomic variations across subjects and to improve signal to noise ratios, a three-dimensional Gaussian filter (FWHM 6 mm) was applied to each scan.

Image analysis

Short-term changes in MOR BP were detected using two sample t-tests between patients receiving TA and SA between experimental conditions in PET1 on a voxel-by-voxel basis using SPM99: (Comparison I = $[TA_{(treatment1-baseline1)} > SA_{(treatment1-baseline1)}]$ and Comparison II = $[SA_{(treatment1-baseline1)} > TA_{(treatment1-baseline1)}]$). Significant effects were detected for each comparison using two separate approaches: 1) an entire image-wide search that was unconstrained by regional predictions and 2) a regional approach that was based on *a priori* hypotheses. For the latter approach, *a priori* regions that had either been previously identified as involved in MOR mediated antinociception in humans (Zubieta et al., 2001, 2005) or PET trials using acupuncture (Biella et al., 2001) were determined using a standard brain atlas. These regions included: cingulate cortex, insula, nucleus accumbens, caudate, putamen, thalamus, hypothalamus, amygdala, and periaqueductal grey. When effects of treatment were observed in these regions we employed an uncorrected statistical threshold of $p<0.001$ with a minimum cluster size of 20 voxels. These typically had z-scores between 3.3 and 4.3 for this analysis. For brain

regions not previously hypothesized, significant regions were identified with a threshold of $p<0.05$ after correction by multiple comparisons using family wise error approach (Friston et al., 1995a,b). These typically had z-scores>4.3 for this analysis.

Long-term changes in MOR BP were also detected using two sample t-tests between patients receiving TA and SA between baseline scans in PET1 versus PET2 on a voxel-by-voxel basis using SPM99: (Comparison I = $[TA_{(baseline2-baseline1)} > SA_{(baseline2-baseline1)}]$ and Comparison II = $[SA_{(baseline2-baseline1)} > TA_{(baseline2-baseline1)}]$). Identical to the short-term changes, significant effects were detected for each comparison using two separate approaches: 1) an entire image-wide search that was unconstrained by regional predictions and 2) a regional approach that was based on *a priori* hypotheses. When effects of treatment were observed in *a priori* regions we employed an uncorrected statistical threshold of $p<0.001$ with a minimum cluster size of 20 voxels. These typically had z-scores between 3.1 and 4.5 for this analysis. For brain regions not previously hypothesized, significant regions were identified with a threshold of $p<0.05$ after correction by multiple comparisons using the family wise error approach (Friston et al., 1995a,b). These typically had z-scores>4.5 for this analysis.

Positive and negative correlations between long-term changes in MOR BP (baseline2–baseline1) and changes in clinical pain (post–pre treatment) were performed using SPM99 again using a voxel-wise whole brain approach and an *a priori* region approach. Only regions showing significance after correction for multiple comparisons (i.e. $p<0.05$ corrected) are reported.

Numerical values for MOR binding were extracted from the image data by averaging the values of voxels contained in an area where significant effects were obtained in the voxel-by-voxel analyses, down to a threshold of $p=0.01$. These values were then entered into SPSS version 14.0 (Chicago, IL) for plotting and assessment of possible outliers.

Treatment

We used an acupuncture treatment protocol previously utilized in a large clinical trial of acupuncture versus sham acupuncture in FM patients (Harris et al., 2005). This protocol was used because: 1) participants could not determine whether they were receiving real or sham acupuncture, and 2) this led to robust effects on chronic pain in both groups. Thus, this seemed an ideal protocol to isolate differences in mechanisms between acupuncture and sham acupuncture, in a group of chronic pain patients. During TA 9 acupuncture needles were inserted: Du20, ear Shenmen, LI4, LI11, Sp6, Liv3, GB34 and bilateral St36 (Fig. 1b). All needles below the neck level were manually manipulated to elicit *De Qi* sensations. SA participants received a non-skin penetrating pricking sensation at 9 non-acupuncture point locations using a previously validated sham procedure (Sherman et al., 2002). The sham locations were within similar body locations as the TA points however they were not on known acupuncture points or meridians. The length of time was similar for needle insertion and manipulation for TA and skin pricking for SA. All participants were blindfolded during each treatment to prevent patient knowledge of treatment assignment.

Clinical pain

Clinical pain was assessed immediately prior to PET1 and PET2 with the Short Form of the McGill Pain Questionnaire (SF MPQ) (Melzack, 1987). The SF MPQ has two subscales that measure "sensory" and "affective" qualities of pain.

Assessment of masking

Following the first PET session, participants were asked to guess which treatment they thought they had been assigned to. The three choices were: 1) "Acupuncture", 2) "Sham Acupuncture", and 3) "Don't know". A Chi-squared test was used to determine whether there was a significant difference between groups (i.e. unmasking or unblinding of the trial).

Results

Short-term differential changes in MOR BP during acupuncture and sham treatment

The design of this trial is depicted in Fig. 1. Short-term differences in MOR BP between TA and SA treatments were examined with two separate comparisons: Comparison I = $[TA_{(treatment1-baseline1)} > SA_{(treatment1-baseline1)}]$ and Comparison II = $[SA_{(treatment1-baseline1)} > TA_{(treatment1-baseline1)}]$. 14 regions were identified as having differences in MOR BP between groups with Comparison I (Table 1 and Fig. 2). No regions were detected with Comparison II that met significance after correction for multiple comparisons (see Supplementary Fig. 1a glass brain results). Inspection of Table 1 and Fig. 2 indicates that treatment differences were attributable largely to increases in MOR BP following TA whereas SA evoked either a small decrease in MOR BP or resulted in no change. Two exceptions were the right amygdala and left insula which showed increases in BP for

Table 1
Regions displaying short-term increases in MOR binding following acupuncture.

Region	MNI coordinates			Voxels	Z	Acupuncture (TA) BP mean(s.e.m.)		Sham (SA) BP mean(s.e.m.)	
	x	y	z			Pre	Post	Pre	Post
Glbl V						0.62 (0.03)	0.61 (0.03)	0.58 (0.03)	0.55 (0.03)
dCC	−1	1	34	178	4.2	0.83 (0.10)	0.95 (0.09)	1.01 (0.12)	0.87 (0.08)
lsgACC	−11	20	−20	120	4.1	1.09 (0.09)	1.18 (0.11)	1.06 (0.09)	0.90 (0.09)
rsgACC	2	35	−20	399	3.9	1.42 (0.07)	1.51 (0.10)	1.39 (0.12)	1.24 (0.10)
lINS	−42	4	−20	540	3.6	0.91 (0.06)	1.22 (0.12)	0.92 (0.07)	1.00 (0.08)
lNAC	−12	12	−6	1004	7.2**	2.38 (0.12)	2.81 (0.23)	2.26 (0.11)	2.22 (0.11)
rCAU	14	16	2	212	3.9	2.12 (0.10)	2.30 (0.14)	1.87 (0.10)	1.81 (0.10)
lCAU	−9	7	6	140	4.1	1.02 (0.13)	1.23 (1.15)	0.98 (0.09)	0.94 (0.07)
dlTHA	11	−26	11	547	5.9**	1.41 (0.14)	1.73 (0.21)	1.36 (0.09)	1.29 (0.10)
vmTHA	2	−9	−5	91	4.9*	0.95 (0.09)	1.29 (0.18)	1.00 (0.12)	1.03 (0.11)
aTHA	−7	−4	10	203	4.4*	1.17 (0.11)	1.46 (0.14)	1.21 (0.10)	1.21 (0.08)
dmTHA	−5	−17	12	54	4.1	1.80 (0.19)	2.08 (0.21)	1.71 (0.15)	1.75 (0.13)
lAMY/tmpole	−26	11	−30	1556	7.1**	1.06 (0.08)	1.39 (0.14)	1.21 (0.09)	1.10 (0.08)
rAMY	18	−4	−25	34	3.3	0.79 (0.07)	1.17 (0.16)	0.88 (0.11)	1.06 (0.12)

**$p<0.001$ corrected; *$p<0.05$ corrected; all other regions $p<0.001$ uncorrected.
Region definitions: (Glbl V) global value; (CC) cingulate cortex; (ACC) anterior cingulate cortex; (INS) insula; (NAC) nucleus accumbens; (CAU) caudate; (THA) thalamus; (AMY) amygdala; (tmpole) temporal pole; (l: left; r: right; a: anterior; d: dorsal; dl: dorsal lateral; dm: dorsal medial; sg: subgenual; vm: ventral medial).

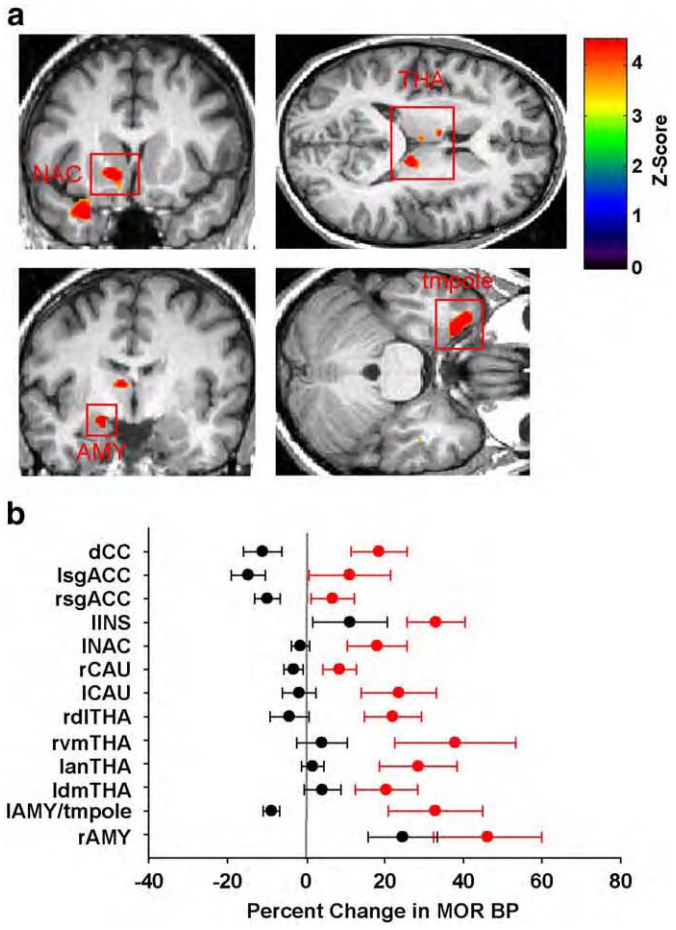


Fig. 2. Differential short-term effects of acupuncture and sham acupuncture on MOR binding. (a) Regions of interest showing increased MOR BP following acupuncture as compared to sham treatment. Upper left: left nucleus accumbens (lNAC), upper right: three thalamic regions (THA), lower left and right: left amygdala (lAMY), and temporal pole (ltmpole) respectively. (b) Percent changes and S.E.M. in MOR BP (treatment1–baseline1) for all regions identified. Red circles (TA) and black circles (SA) represent group mean values with standard error bars. Overall acupuncture resulted in increases in MOR BP with sham treatment resulting largely in either no change or small decreases in BP.

both groups, albeit larger increases for traditional acupuncture. Within the regions identified, the cingulate cortex, the nucleus accumbens, the thalamic nuclei, amygdala, and the temporal pole form part of an endogenous opioid circuit known to participate in the regulation of sensory and affective qualities of pain, as well as in emotional responses in humans (Zubieta et al., 2003a, 2001; Kennedy et al., 2006; Zubieta et al., 2003b).

To investigate whether the observed differences between TA and SA could be due to baseline differences between treatment groups, we compared baseline MOR BP values for the above 14 regions. None of the regions of interest (ROIs) showed significant baseline differences between groups in MOR BP (all $p>0.10$), confirming that the observed binding changes were due largely to effects during treatment.

Long-term differential changes in MOR BP following acupuncture and sham treatment

Long-term differences in MOR BP between TA and SA treatments were likewise examined with two separate comparisons: Comparison I = $[TA_{(baseline2-baseline1)} > SA_{(baseline2-baseline1)}]$ and Comparison II = $[SA_{(baseline2-baseline1)} > TA_{(baseline2-baseline1)}]$. 10 regions were identified as having differences in MOR BP between groups with Comparison I (Table 2 and Fig. 3). No regions were detected with Comparison II that met significance after correction for multiple comparisons (see Supplementary Fig. 1b for glass brain results). Inspection of Table 2 and Fig. 3 indicates that treatment differences were again largely attributable to increases in MOR BP following TA whereas SA evoked either small reductions in MOR BP or resulted in no change. Similar to the short-term effects, regions identified as showing increases in MOR BP included the amygdala, the cingulate cortex, the caudate, the putamen, and the temporal pole.

To investigate whether the observed differences following TA and SA could be due to baseline differences, between treatment groups, we compared baseline MOR BP values for the above 10 regions. None of the ROIs showed significant baseline differences in MOR BP (all $p>0.15$) again supporting the conclusion that they were largely due to effects following long-term treatment.

Changes in clinical pain

Clinical pain intensity was assessed prior to both PET imaging sessions. Significant reductions in pain were observed for the entire cohort for the total score of the Short Form of the McGill Pain Questionnaire (SF MPQ Total; mean diff(SD) treatment − baseline; −3.45(7.39), $p<0.05$) and trended towards significance for the sensory and pain affect subscales (Sensory Score: −2.65(5.98), $p=0.06$; Affective Score: −0.80(2.26), $p=0.13$). Both TA and SA resulted in clinically meaningful reductions in pain (SF MPQ Total Score mean diff(SD); TA: −4.00(6.72); SA: −2.90(8.33)), however there were no statistically significant differences in pain reduction between TA and SA ($p>0.50$).

Table 2
Regions displaying long-term increases in MOR binding following acupuncture.

Region	MNI coordinates			Voxels	*Z*	Acupuncture (TA) BP mean(s.e.m.)		Sham (SA) BP mean(s.e.m.)	
	x	*y*	*z*			Pre	Post	Pre	Post
Glbl V						0.62 (0.03)	0.65 (0.03)	0.58 (0.03)	0.59 (0.04)
DLPFC	−30	29	26	351	3.3	0.63 (0.04)	0.80 (0.09)	0.79 (0.11)	0.74 (0.10)
ldCC	−3	−16	57	225	3.3	0.90 (0.06)	1.02 (0.05)	0.92 (0.11)	0.82 (0.07)
rdCC	10	−8	54	192	3.1	0.76 (0.07)	0.94 (0.08)	0.71 (0.05)	0.67 (0.06)
dACC	0	0	33	185	3.7	0.74 (0.10)	0.89 (0.09)	0.93 (0.11)	0.81 (0.08)
pgACC(1)	13	42	−1	628	3.3	0.92 (0.08)	1.16 (0.10)	0.87 (0.06)	0.87 (0.08)
pgACC(2)	14	44	12	114	3.2	0.91 (0.09)	1.14 (0.10)	0.81 (0.08)	0.81 (0.09)
PUT	20	12	−12	158	3.2	1.47 (0.07)	1.66 (0.07)	1.48 (0.08)	1.45 (0.08)
CAU	−8	15	4	23	3.2	1.11 (0.15)	1.31 (0.15)	1.05 (0.12)	1.03 (0.13)
AMY/tmpole	−30	11	−29	2417	4.8*	1.08 (0.08)	1.24 (0.09)	1.27 (0.12)	1.09 (0.07)
tmpole	−39	15	−28	1037	4.7*	1.27 (0.06)	1.53 (0.09)	1.27 (0.09)	1.20 (0.08)

*$p<0.05$ corrected; all other regions $p<0.001$ uncorrected.
Region definitions: (Glbl V) global value; (DLPFC) dorsal lateral prefrontal cortex; (CC) cingulate cortex; (ACC) anterior cingulate cortex; (CAU) caudate; (PUT) putamen; (AMY) amygdala; (tmpole) temporal pole; (l: left; r: right; d: dorsal; pg: perigenual).

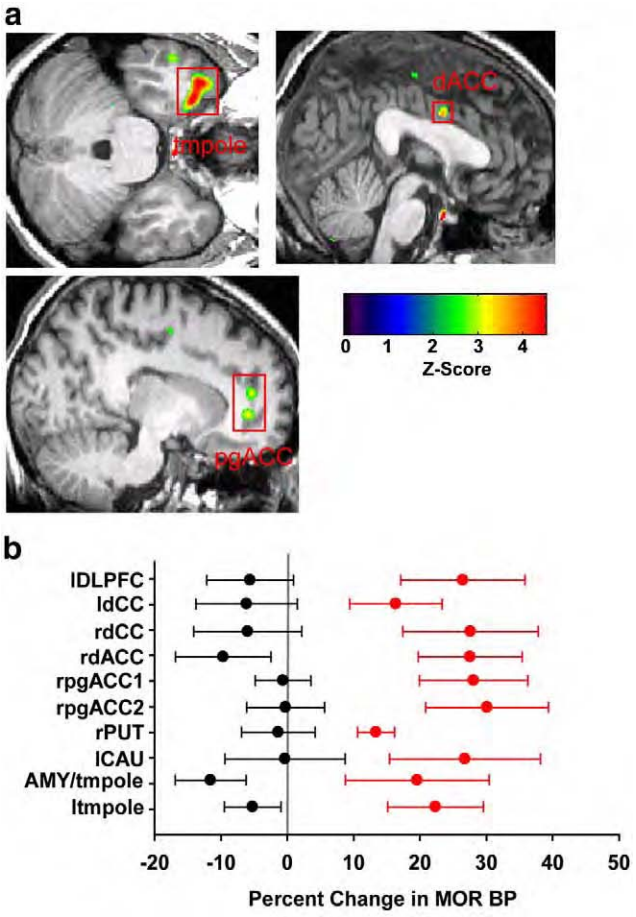


Fig. 3. Differential long-term effects of acupuncture and sham acupuncture on MOR binding. (a) Regions of interest showing increased MOR BP following acupuncture as compared to sham treatment. Upper left: temporal pole (ltmpole), upper right: dorsal anterior cingulate cortex (dACC), lower left: two perigenual anterior cingulate regions (pgACC). (b) Percent changes and S.E.M. in MOR BP (baseline2–baseline1) for all regions identified. Red circles (TA) and black circles (SA) represent group mean values with standard error bars. Overall acupuncture resulted in an increase in MOR BP whereas sham treatment resulted in either no change or a decrease in binding ability.

Changes in MOR binding are associated with changes in clinical pain

To investigate the analgesic relevance of the changes in MOR BP following TA, we correlated post–pre treatment changes in the SF MPQ Total score with the observed percent changes in MOR BP (i.e. baseline2–baseline1) within participants that were treated with traditional acupuncture. Seven regions were identified as showing a negative correlation between changes in clinical pain and changes in MOR BP (Table 3 and Fig. 4). Among these regions the thalamus, the cingulate, and the insula are known to play significant roles in processing and modulating pain sensations. Other regions included the caudate, the putamen and the temporal pole. These regions have been identified in other studies as showing differential response to acupuncture and sham treatment (Napadow et al., 2005; Hui et al., 2000). No regions were identified in the TA group as showing significant positive correlations between changes in MOR BP and changes in pain (see Supplementary Fig. 1c for glass brain results). However the dorsolateral prefrontal cortex, which showed decreases in MOR BP in the SA group (see Fig. 3) had a significant positive correlation with pain reduction following sham treatment ($r = 0.69$; $p = 0.027$). Individuals with greater reductions in MOR BP within this region, had greater reductions in clinical pain.

Assessment of masking

To determine if the observed changes in MOR binding between groups could have resulted from participants knowing what treatment they received (i.e. unmasking of the trial), we asked all patients to guess what group they thought they were assigned to after the first PET imaging session. Participant guesses were consistent across the two groups. Four subjects in the TA group and three subjects in the SA group thought that they received traditional acupuncture. One participant in the SA group and two participants in the TA group thought that they received sham acupuncture, and four participants in the TA and six in the SA group did not know what treatment they received. These two distributions were not statistically different (Chi-Square value = 0.88; $p = 0.65$).

Discussion

We provide the first direct evidence of short- and long-term effects of acupuncture therapy on central MOR binding availability in chronic pain patients. Overall we find that traditional acupuncture therapy evokes an increase in MOR availability over both short and long periods. These changes were absent in sham treated patients where either no change was detected or decreases in MOR BP were observed. Reduction in central MOR BP during SA is consistent with increased endogenous opioid release during placebo administration (Zubieta et al., 2005; Scott et al., 2008). For both short- and long-term effects of TA, areas showing increases in BP included a number of brain regions classically implicated in the regulation of pain and stress in humans (Zubieta et al., 2001, 2003b), such as the amygdala, the dorsal and perigenual anterior cingulate, and the insular cortex. Other regions also shown to be involved in responses to pain and other salient stimuli and where TA induced significant effects on MOR BP included the nucleus accumbens, the caudate, and the putamen (Gear and Levine, 1995; Scott et al., 2006). The nucleus accumbens and the dorsal cingulate are both regions that we identified previously as showing reduced binding in FM patients as compared to controls (Harris et al., 2007). Finally, a region of the temporal pole showed increases in binding following TA for both short and long time periods, and displayed a significant negative correlation with changes in clinical pain. This temporal pole region has previously been identified as showing responsiveness to negative mood (Kennedy et al., 2006; Zubieta et al., 2003b) as well as acupuncture treatment (Napadow et al., 2005; Hui et al., 2000).

Our findings of widespread increases in regional MOR binding availability are consistent with a previous trial of acupuncture in rodents showing that acupuncture induces an increase in the number of central MOR binding sites following treatment (Gao et al., 1997). For changes that arise following long-term therapy, this could involve increased transcription and translation of MORs and their subsequent insertion into the plasma membrane. Indeed acupuncture treatment has been shown to modulate the levels of transcription factors within

Table 3
Regions displaying negative correlation between MOR binding changes and changes in clinical pain following acupuncture.

Region	MNI coordinates			Voxels	*Z*	*r*
	x	*y*	*z*			
ldCC	−15	10	36	315	4.7	−0.50
raINS	36	24	−3	773	3.6	−0.78
lCAU	−7	10	2	686	6.8**	−0.70
rPUT-rCAU	19	7	−4	2096	6.0**	−0.76
lmTHA	−4	−12	11	1008	5.4*	−0.65
ltmpole	−29	15	−34	1310	6.3**	−0.71
rtmpole	26	11	−36	924	5.8**	−0.60

**$p<0.001$ corrected; *$p<0.005$ corrected; all other regions $p<0.05$ corrected.
Patients with greater increases in MOR BP displayed greater reductions in clinical pain.

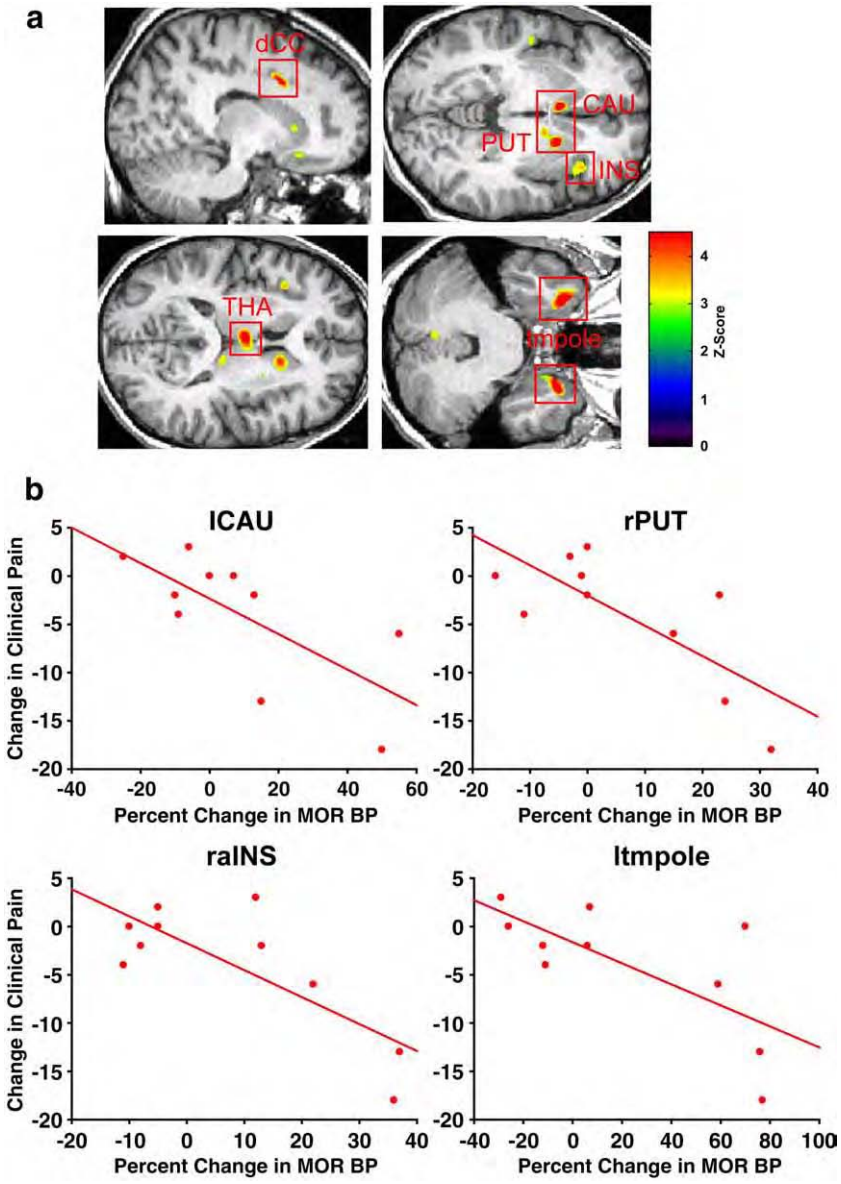


Fig. 4. Long-term increases in MOR binding following acupuncture are associated with reductions in clinical pain. (a) Regions of interest showing negative correlations between changes in MOR BP (baseline2–baseline1) and changes in clinical pain (pain assessment2–pain assessment1) following acupuncture. Upper left: left dorsal cingulate cortex (ldCC), upper right: left caudate (lCAU), right putamen (rPUT), and right anterior insula (raIns), lower left: left medial thalamus (lmTHA), lower right: bilateral temporal pole (tmpole). (b) Scatter plots of percent changes in MOR BP (post–pre) and changes in clinical pain (post–pre) for four regions depicted in A.

the central nervous system (Lao et al., 2004). However this explanation does not address the relatively rapid increases in MOR BP that we observe (i.e. within 45 min) following needle insertion. One possible explanation originates from animal and tissue preparations where increases in the plasma membrane expression of all three classes of opioid receptors have been shown to occur in neurons following excitation. The sub-cellular localization of μ- (Browning et al., 2004), κ- (Shuster et al., 1999), and Δ- (Bao et al., 2003) opioid receptors all appear to be dynamically regulated by neural activity. Following neuronal excitation, all three classes of receptors have been shown to be trafficked to the plasma membrane within the time frame that we observe our short-term acupuncture effects (i.e. within 45 min). This type of regulation of glutamate receptors has been observed during long-term potentiation (LTP) and long-term depression (LTD) where neuronal activity modulates receptor expression at the plasma membrane (Malenka, 2003). Interestingly a recent study by Xing et al. (2007) suggests that acupuncture can also induce LTD in the spinal cord in a rat model of chronic pain and this depression is abolished by the opioid receptor antagonist naloxone. LTD-type modulation of MORs and subsequent changes in synaptic strength could function as a mechanism for acupuncture analgesia given the lasting effects of acupuncture observed here and in other clinical trials (Brinkhaus et al., 2006; Linde et al., 2005; Melchart et al., 2005; Witt et al., 2005).

Another intriguing result from the present study is that although MOR BP values were differentially altered by TA and SA, reduction in clinical pain was similar between groups. In a clinical trial, when an active treatment does not exhibit superior efficacy to a sham or placebo, the active treatment is assumed to be ineffective and only operating via a placebo effect. However this study suggests that this may be an erroneous conclusion. In this instance, our non-insertion sham procedure evoked a similar reduction in pain as our true acupuncture and we speculate that this occurred via a different mechanism. The analgesic effects of SA could have been due to regional reductions in MOR BP, consistent with activation of this class of receptors during placebo effects (Zubieta et al., 2005), whereas TA

evoked an increase in receptor binding availability. This interpretation is entirely consistent with the observed positive correlation between decreases in MOR BP within the dorsolateral prefrontal cortex and decreased pain in the SA group. These reductions in MOR BP may also be operating in TA however these effects may be "masked" by the increases in receptor binding availability noted above.

Finally we explored the relationship between increases in MOR BP following acupuncture and subsequent changes in clinical pain. We found that many of the same regions showing increases in binding following acupuncture therapy were also associated with reductions in clinical pain. Since our previous study found reductions in MOR BP in FM patients (Harris et al., 2007), acupuncture may act to increase or "normalize" MOR binding ability in FM patients to levels that are more representative of pain free controls.

To determine if participants could tell the difference in treatments and unblind the trial, we asked our participants to guess which treatment they thought they received following the first PET imaging session. We found that both groups had similar guesses for their treatment assignments suggesting our results were not likely to be explained by participant knowledge of treatment assignment.

In this work some participants were taking medications, however we monitored closely their usage (see Supplementary Table 2). Patients remained on stable doses of existing medications for the entire duration of the study. Therefore, medications are unlikely to represent a confounding factor in the analyses presented. Any medication confound would be operative in both pre- and post-treatment scans as well as for TA and SA groups.

Our sham intervention was performed on non-acupuncture points and did not involve skin penetration. Therefore our differential effects of TA and SA may be due to point location and/or skin penetration. Future studies are needed to determine if the differential effects on MOR BP are due to either skin penetration or acupuncture point stimulation or a combination of both.

Overall our data strongly imply divergent opioid receptor mechanisms in acupuncture and sham acupuncture therapy. Although the fundamental mechanisms underlying these processes await further investigation, central opioid receptors appear to be involved in both treatments, albeit with differing effects within the same brain structures. Greater insight into these effects may be obtained in animal models of chronic pain disorders.

Acknowledgments

This work was funded by Department of Army grants DAMD (17/002-0018 to D.J.C. and W81XWH-07-2-0050 to R.E.H.) and National Institutes of Health (M01-RR000042 to R.E.H.; R01 AT 001415 to J.K.Z., K01 AT01111-01 to R.E.H., and K01-AT002166 and P01-AT002048 to V.N.).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.05.083.

References

Amanzio, M., Benedetti, F., 1999. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. J. Neurosci. 19, 484–494.

Bao, L., Jin, S.X., Zhang, C., Wang, L.H., Xu, Z.Z., Zhang, F.X., Wang, L.C., Ning, F.S., Cai, H.J., Guan, J.S., Xiao, H.S., Xu, Z.Q., He, C., Hokfelt, T., Zhou, Z., Zhang, X., 2003. Activation of delta opioid receptors induces receptor insertion and neuropeptide secretion. Neuron 37, 121–133.

Benedetti, F., Amanzio, M., 1997. The neurobiology of placebo analgesia: from endogenous opioids to cholecystokinin. Prog. Neurobiol. 52, 109–125.

Biella, G., Sotgiu, M.L., Pellegata, G., Paulesu, E., Castiglioni, I., Fazio, F., 2001. Acupuncture produces central activations in pain regions. NeuroImage 14, 60–66.

Brinkhaus, B., Witt, C.M., Jena, S., Linde, K., Streng, A., Wagenpfeil, S., Irnich, D., Walther, H.U., Melchart, D., Willich, S.N., 2006. Acupuncture in patients with chronic low back pain: a randomized controlled trial. Arch. Intern. Med. 166, 450–457.

Browning, K.N., Kalyuzhny, A.E., Travagli, R.A., 2004. μ-opioid receptor trafficking on inhibitory synapses in the rat brainstem. J. Neurosci. 24, 7344–7352.

Chen, X.H., Geller, E.B., Adler, M.W., 1996. Electrical stimulation at traditional acupuncture sites in periphery produces brain opioid-receptor-mediated antinociception in rats. J. Pharmacol. Exp. Ther. 277, 654–660.

Dougherty, D.D., Kong, J., Webb, M., Bonab, A.A., Fischman, A.J., Gollub, R.L., 2008. A combined [11C]diprenorphine PET study and fMRI study of acupuncture analgesia. Behav. Brain Res. 193, 63–68.

Friston, K.J., Frith, C.D., Frackowiak, R.S., Turner, R., 1995a. Characterizing dynamic brain responses with fMRI: a multivariate approach. NeuroImage 2, 166–172.

Friston, K.J., Holmes, A.P., Poline, J.B., Grasby, P.J., Williams, S.C., Frackowiak, R.S., Turner, R., 1995b. Analysis of fMRI time-series revisited. NeuroImage 2, 45–53.

Gabilondo, A.M., Meana, J.J., Garcia-Sevilla, J.A., 1995. Increased density of μ-opioid receptors in the postmortem brain of suicide victims. Brain Res. 682, 245–250.

Gao, M., Wang, M., Li, K., He, L., 1997. Changes of μ-opioid receptor binding sites in rat brain following electroacupuncture. Acupunct. Electro-ther. Res. 22, 161–166.

Gear, R.W., Levine, J.D., 1995. Antinociception produced by an ascending spino-supraspinal pathway. J. Neurosci. 15, 3154–3161.

Gracely, R.H., Petzke, F., Wolf, J.M., Clauw, D.J., 2002. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum. 46, 1333–1343.

Gross-Isseroff, R., Dillon, K.A., Israeli, M., Biegon, A., 1990. Regionally selective increases in μ-opioid receptor density in the brains of suicide victims. Brain Res. 530, 312–316.

Harris, R.E., Tian, X., Williams, D.A., Tian, T.X., Cupps, T.R., Petzke, F., Groner, K.H., Biswas, P., Gracely, R.H., Clauw, D.J., 2005. Treatment of fibromyalgia with formula acupuncture: investigation of needle placement, needle stimulation, and treatment frequency. J. Altern. Complement. Med. 11, 663–671.

Harris, R.E., Clauw, D.J., Scott, D.J., McLean, S.A., Gracely, R.H., Zubieta, J.K., 2007. Decreased central μ-opioid receptor availability in fibromyalgia. J. Neurosci. 27, 10000–10006.

He, L.F., Lu, R.L., Zhuang, S.Y., Zhang, X.G., Pan, X.P., 1985. Possible involvement of opioid peptides of caudate nucleus in acupuncture analgesia. Pain 23, 83–93.

Ho, W.K., Wen, H.L., 1989. Opioid-like activity in the cerebrospinal fluid of pain patients treated by electroacupuncture. Neuropharmacology 28, 961–966.

Hui, K.K., Liu, J., Makris, N., Gollub, R.L., Chen, A.J., Moore, C.I., Kennedy, D.N., Rosen, B.R., Kwong, K.K., 2000. Acupuncture modulates the limbic system and subcortical gray structures of the human brain: evidence from fMRI studies in normal subjects. Hum. Brain Mapp. 9, 13–25.

Hui, K.K., Liu, J., Marina, O., Napadow, V., Haselgrove, C., Kwong, K.K., Kennedy, D.N., Makris, N., 2005. The integrated response of the human cerebro-cerebellar and limbic systems to acupuncture stimulation at ST 36 as evidenced by fMRI. NeuroImage 27, 479–496.

Jewett, D.M., 2001. A simple synthesis of [11C]carfentanil using an extraction disk instead of HPLC. Nucl. Med. Biol. 28, 733–734.

Joshi, A., Fessler, J.A., Koeppe, R.A., 2008. Improving PET receptor binding estimates from Logan plots using principal component analysis. J. Cereb. Blood Flow Metab. 28, 852–865.

Kennedy, S.E., Koeppe, R.A., Young, E.A., Zubieta, J.K., 2006. Dysregulation of endogenous opioid emotion regulation circuitry in major depression in women. Arch. Gen. Psychiatry 63, 1199–1208.

Lao, L., Zhang, R.X., Zhang, G., Wang, X., Berman, B.M., Ren, K., 2004. A parametric study of electroacupuncture on persistent hyperalgesia and Fos protein expression in rats. Brain Res. 1020, 18–29.

Levine, J.D., Gordon, N.C., Fields, H.L., 1978. The mechanism of placebo analgesia. Lancet 2, 654–657.

Linde, K., Streng, A., Jurgens, S., Hoppe, A., Brinkhaus, B., Witt, C., Wagenpfeil, S., Pfaffenrath, V., Hammes, M.G., Weidenhammer, W., Willich, S.N., Melchart, D., 2005. Acupuncture for patients with migraine: a randomized controlled trial. JAMA 293, 2118–2125.

Logan, J., Fowler, J.S., Volkow, N.D., Wang, G.J., Ding, Y.S., Alexoff, D.L., 1996. Distribution volume ratios without blood sampling from graphical analysis of PET data. J. Cereb. Blood Flow Metab. 16, 834–840.

Malenka, R.C., 2003. Synaptic plasticity and AMPA receptor trafficking. Ann. N.Y. Acad. Sci. 1003, 1–11.

Melchart, D., Streng, A., Hoppe, A., Brinkhaus, B., Witt, C., Wagenpfeil, S., Pfaffenrath, V., Hammes, M., Hummelsberger, J., Irnich, D., Weidenhammer, W., Willich, S.N., Linde, K., 2005. Acupuncture in patients with tension-type headache: randomised controlled trial. BMJ 331, 376–382.

Melzack, R., 1987. The short-form McGill Pain Questionnaire. Pain 30, 191–197.

Minoshima, S., Koeppe, R.A., Mintun, M.A., Berger, K.L., Taylor, S.F., Frey, K.A., Kuhl, D.E., 1993. Automated detection of the intercommissural line for stereotactic localization of functional brain images. J. Nucl. Med. 34, 322–329.

Napadow, V., Makris, N., Liu, J., Kettner, N.W., Kwong, K.K., Hui, K.K., 2005. Effects of electroacupuncture versus manual acupuncture on the human brain as measured by fMRI. Hum. Brain Mapp. 24, 193–205.

Napadow, V., Kettner, N., Liu, J., Li, M., Kwong, K.K., Vangel, M., Makris, N., Audette, J., Hui, K.K., 2007. Hypothalamus and amygdala response to acupuncture stimuli in carpal tunnel syndrome. Pain 130 (3), 254–266.

Pert, A., Dionne, R., Ng, L., Bragin, E., Moody, T.W., Pert, C.B., 1981. Alterations in rat central nervous system endorphins following transauricular electroacupuncture. Brain Res. 224, 83–93.

Pomeranz, B., Chiu, D., 1976. Naloxone blockade of acupuncture analgesia: endorphin implicated. Life Sci. 19, 1757–1762.

Scott, D.J., Heitzeg, M.M., Koeppe, R.A., Stohler, C.S., Zubieta, J.K., 2006. Variations in the human pain stress experience mediated by ventral and dorsal basal ganglia dopamine activity. J. Neurosci. 26, 10789–10795.
Scott, D.J., Stohler, C.S., Egnatuk, C.M., Wang, H., Koeppe, R.A., Zubieta, J.K., 2008. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. Arch. Gen. Psychiatry 65, 220–231.
Sherman, K.J., Hogeboom, C.J., Cherkin, D.C., Deyo, R.A., 2002. Description and validation of a noninvasive placebo acupuncture procedure. J. Altern. Complement. Med. 8, 11–19.
Shuster, S.J., Riedl, M., Li, X., Vulchanova, L., Elde, R., 1999. Stimulus-dependent translocation of kappa opioid receptors to the plasma membrane. J. Neurosci. 19, 2658–2664.
Stux, G., Hammerschlag, R., 2001. Clinical Acupuncture: Scientific Basis. Springer, New York.
Witt, C., Brinkhaus, B., Jena, S., Linde, K., Streng, A., Wagenpfeil, S., Hummelsberger, J., Walther, H.U., Melchart, D., Willich, S.N., 2005. Acupuncture in patients with osteoarthritis of the knee: a randomised trial. Lancet 366, 136–143.
Wolfe, F., Smythe, H.A., Yunus, M.B., Bennett, R.M., Bombardier, C., Goldenberg, D.L., Tugwell, P., Campbell, S.M., Abeles, M., Clark, P., 1990. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. 33, 160–172.
Wolfe, F., Ross, K., Anderson, J., Russell, I.J., Hebert, L., 1995. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum. 38, 19–28.
Xing, G.G., Liu, F.Y., Qu, X.X., Han, J.S., Wan, Y., 2007. Long-term synaptic plasticity in the spinal dorsal horn and its modulation by electroacupuncture in rats with neuropathic pain. Exp. Neurol. 208, 323–332.
Zubieta, J.K., Smith, Y.R., Bueller, J.A., Xu, Y., Kilbourn, M.R., Jewett, D.M., Meyer, C.R., Koeppe, R.A., Stohler, C.S., 2001. Regional μ-opioid receptor regulation of sensory and affective dimensions of pain. Science 293, 311–315.
Zubieta, J.K., Heitzeg, M.M., Smith, Y.R., Bueller, J.A., Xu, K., Xu, Y., Koeppe, R.A., Stohler, C.S., Goldman, D., 2003a. COMT val158met genotype affects μ-opioid neurotransmitter responses to a pain stressor. Science 299, 1240–1243.
Zubieta, J.K., Ketter, T.A., Bueller, J.A., Xu, Y., Kilbourn, M.R., Young, E.A., Koeppe, R.A., 2003b. Regulation of human affective responses by anterior cingulate and limbic μ-opioid neurotransmission. Arch. Gen. Psychiatry 60, 1145–1153.
Zubieta, J.K., Bueller, J.A., Jackson, L.R., Scott, D.J., Xu, Y., Koeppe, R.A., Nichols, T.E., Stohler, C.S., 2005. Placebo effects mediated by endogenous opioid activity on μ-opioid receptors. J. Neurosci. 25, 7754–7762.

PAIN® 143 (2009) 262–267

PAIN®

www.elsevier.com/locate/pain

No consistent difference in gray matter volume between individuals with fibromyalgia and age-matched healthy subjects when controlling for affective disorder

Michael C. Hsu [a,*], Richard E. Harris [b], Pia C. Sundgren [c], Robert C. Welsh [c,f], Carlo R. Fernandes [d], Daniel J. Clauw [b,e,f], David A. Williams [b,e,f,g]

[a] Department of Physical Medicine & Rehabilitation, University of Michigan Chronic Pain & Fatigue Research Center, 24 Frank Lloyd Wright Drive, Lobby M, P.O. Box 385, Ann Arbor, MI 48106, USA
[b] Department of Anesthesiology, University of Michigan, Ann Arbor, MI, USA
[c] Department of Radiology, University of Michigan, Ann Arbor, MI, USA
[d] College of Literature, Sciences, and the Arts, University of Michigan, Ann Arbor, MI, USA
[e] Department of Medicine, University of Michigan, Ann Arbor, MI, USA
[f] Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA
[g] Department of Psychology, University of Michigan, Ann Arbor, MI, USA

ARTICLE INFO

Article history:
Received 9 July 2008
Received in revised form 13 January 2009
Accepted 16 March 2009

Keywords:
Fibromyalgia
Voxel-based morphometry
MRI
Gray matter
Depression
Pain

ABSTRACT

Fibromyalgia (FM) is thought to involve abnormalities in central pain processing. Recent studies involving small samples have suggested alterations in gray matter volume (GMV) in brains of FM patients. Our objective was to verify these findings in a somewhat larger sample using voxel-based morphometry (VBM), while controlling for the presence of affective disorders (AD). T1-weighted magnetic resonance image (MRI) brain scans were obtained on 29 FM patients with AD, 29 FM patients without AD, and 29 age-matched healthy controls (HCs) using a 3T scanner. Segmentation, spatial normalization, and volumetric modulation were performed using an automated protocol within SPM5. Smoothed gray matter segments were entered into a voxel-wise one-way ANOVA, and a search for significant clusters was performed using thresholding methods published in previous studies (whole-brain threshold of $p < .05$ correcting for multiple comparisons; region-of-interest (ROI) threshold of $p \leqslant .001$ uncorrected, or $p < .05$ small-volume corrected). The whole-brain analysis did not reveal any significant clusters. ROI-based analysis revealed a significant difference in left anterior insula GMV among the three groups ($xyz = \{-28, 21, 9\}$; $p = .026$, corrected). However, on post-hoc testing, FM patients without AD did not differ significantly from HC with respect to mean GMV extracted from this cluster. A significant negative correlation was found between mean cluster GMV and scores of trait anxiety (State-Trait Personality Inventory, Trait Anxiety scale; rho = −.470, $p < .001$). No other significant clusters were found on ROI-based analysis. Our results emphasize the importance of correcting for AD when carrying out VBM studies in chronic pain.

1. Introduction

Fibromyalgia (FM) affects 0.5–4% of the population in developed countries [14,24], and is defined as chronic widespread pain and tenderness in at least 11 of 18 tender points [26]. Individuals with FM are more likely to also meet criteria for chronic fatigue syndrome, irritable bowel syndrome, temporomandibular joint disorder, vulvodynia, and migraine than the general population [11]. Mechanisms of central augmentation of pain and sensory processing are thought to account for the pathophysiology of FM and related conditions [15].

Evidence of abnormal CNS processing in FM can be found in a number of functional neuroimaging studies, including altered resting and stimulus-evoked regional cerebral blood flow in pain and emotional processing regions such as the thalamus, somatosensory cortex, insula, and anterior cingulate cortex [25]. In contrast to functional neuroimaging, structural neuroimaging approaches – such as voxel-based morphometry (VBM) – use differences in gray matter volume (GMV) or density to support hypotheses regarding CNS function, and may reflect trait rather than state characteristics of the brain. With recent improvements in computer processing speed, the automated process of VBM has allowed for fast, reliable calculations of GMV in large samples of subjects [2].

In recent years, VBM has been used to study differences in GMV associated with various pain conditions, including migraine [23],

* Corresponding author. Tel.: +1 734 997 7409; fax: +1 734 998 6900.
E-mail address: michsu@umich.edu (M.C. Hsu).

0304-3959/$36.00
doi:10.1016/j.pain.2009.03.017

tension headache [17], chronic back pain [1,16], and FM [12,18]. The two studies published to date in FM patients reported global and/or regional GMV differences between patients and controls. However, the sample sizes were modest (⩽20 in the FM group), and there were no common regions of increased or decreased GMV between the two studies. Furthermore, while both studies addressed depression as a potential confounding variable, one study did not account for less-severe depressive disorders such as dysthymia [12], and the other study did not find any significant GMV differences at the whole-brain level after controlling for depression [18].

In the present study, we applied VBM methodology to a sample of 58 FM patients and 29 age-matched healthy controls, to look for regions of increased or decreased GMV associated with FM, and attempted to replicate the previously published findings. We used statistical thresholds identical to those published in previous studies [12,18]. We then tested whether the results changed when controlling for AD. We hypothesized that one or more regional GMV changes previously reported to be associated with FM would be replicated in this study. We also hypothesized that, even when controlling for AD, FM patients would still exhibit differences in global and/or regional GMV within pain-related brain regions relative to controls.

2. Methods

2.1. Participants

All subjects with FM who were enrolled in two ongoing non-pharmacological clinical trials were considered for the present analyses. Healthy controls were obtained from the same studies, and also from a previous cross-sectional study performed at our center. At the time of data collection, all FM patients had met 1990 American College of Rheumatology criteria for FM [26], with mean pain duration of 12.8 years (SD = 8.3). No healthy controls had met these criteria, nor did they meet criteria for chronic regional pain (i.e., tension headaches, chronic low back pain, irritable bowel syndrome, or chronic pelvic pain). All subjects were right-handed women between ages 18 and 65. All subjects gave written informed consent, the study protocol was approved by the University of Michigan Institutional Review Board, and all procedures performed in compliance with the Helsinki Declaration.

Affective disorder (AD) was defined as current major depressive episode, bipolar disorder, dysthymia, or general anxiety disorder (according to *Diagnostic and Statistical Manual of the American Psychiatric Association IV* criteria) as determined upon subject enrollment using a structured interview [19]. Patients with a history of clinical depression according to medical records; and/or patient-reported use of antidepressants to treat depression or anxiety, were also considered to have AD. Individuals with AD were excluded from the healthy control group. Individuals with severe psychiatric illness (current schizophrenia, major depression with suicidal ideation, substance abuse within two years), were excluded from all groups.

A total of 29 FM patients with AD (FM+AD), 29 FM patients without AD (FM−AD), and 29 healthy controls were included in the analysis. The groups were individually matched by age, with an overall difference of no more than three years across each matched trio.

2.2. Neuroimaging and analysis

2.2.1. Image acquisition

High-resolution anatomical magnetic resonance image (MRI) scans were obtained on all subjects using the same 3-Tesla scanner (Signa LX, General Electric, Milwaukee, USA). Images were acquired by using spoiled gradient-recalled acquisition in steady state (SPGR) imaging (repetition time, 10.5 ms; echo time, 3.4 ms; flip angle, 20°; field of view 24 cm, number of contiguous images, 106; in-plane resolution .9375 × .9375 mm, slice thickness, 1.5 mm). The resulting voxel dimension was of sufficiently high resolution to permit accurate gray matter segmentation [2].

2.2.2. VBM protocol

Data pre-processing and analysis were performed using SPM5 (Wellcome Department of Cognitive Neurology, London, UK) on the Matlab version 6.5 (MathWorks, Natick, MA) platform. Each image was inspected for reconstruction artifacts, and individually corrected for signal inhomogeneity using an automated Matlab protocol developed by G. Glover and K. Christoff (http://rsl.stanford.edu/glover/). Spatial normalization, segmentation, and volumetric modulation were performed using the automated VBM5 toolbox (C. Gaser, Structural Brain Imaging Group, Department of Psychiatry, University of Jena; http://dbm.neuro.uni-jena.de/vbm/) within the SPM5 environment. The toolbox employs a Hidden Markov Random Field Model in the procedure to segment each image into gray matter, white matter, and cerebrospinal fluid. The toolbox then normalizes the gray matter segment of each image to the International Consortium for Brain Mapping (ICBM) 152 template (Montreal Neurological Institute; MNI), and performs a modulation step to scale each voxel value according to the subject's total intracranial volume (TIV), as well as the regional gray matter volume (GMV) expansion/contraction that occurs during nonlinear transformation. TIV and global GMV were obtained for each image, using the "Calculate raw volumes" feature of VBM5. Gray matter image segments were inspected for segmentation artifacts, then smoothed using an isotropic Gaussian kernel of 10 mm full-width half-maximum (FWHM), to accommodate individual differences in sulcal and gyral anatomy, and to meet the distributional assumptions of the general linear models necessary for statistical analysis. This is the same smoothing kernel as was used in the previous studies ([12,18]; a comparison of methods used in the two previous studies and in the present study is shown in Table 1).

2.2.3. Voxel-wise comparison of GMV between FM patients and healthy controls

The normalized, modulated, and smoothed gray matter image segments in each group were entered into a voxel-wise one-way ANOVA in SPM5, with a null hypothesis of no GMV difference among the three groups (FM+AD, FM−AD, and HC). Because the modulation step reintroduces information about the subject's TIV prior to normalization, TIV was included as a covariate. An absolute threshold mask of 0.20 was used (identical to the threshold used in the previous study [18]), to avoid possible edge effects around the border between gray and white matter. Due to the occasional presence of susceptibility artifacts at the base of the brain in our sample, an explicit mask was also used to exclude all voxels inferior to $z = -22$ (Talairach space).

A whole brain search for significant clusters was performed using the previously published voxel-wise threshold of $p < .05$ corrected for multiple comparisons [12,18]. In addition, an ROI-based search using all *a priori* anatomically defined ROIs from the two previously published studies (Table 2) was conducted. For the ROI-based search, all clusters with either a voxel-level $p < .05$ (small-volume and family-wise error corrected using masks from the MarsBar ROI toolbox [6], accessible at http://marsbar.sourceforge.net/) or an uncorrected voxel-level $p < .001$ were considered significant. Since post-hoc tests were not available for SPM5 at the time of these analyses, post-hoc analysis was performed using between-group contrasts on the F map to determine the peak significance value of any voxels within the cluster, and a

Table 1
Differences among VBM studies of FM patients vs. healthy controls.

Study	*N* (FM/HC)	Handedness	Mean age (FM/HC)	Mean duration of pain, FM subjects	Screening tool for affective disorder
Kuchinad et al. [12]	10/10	Not reported	52/45[a]	6.85 yrs (time since diagnosis)	DSM-IV criteria (MDD)
Schmidt-Wilcke et al. [18]	20/22	Not reported	53.6/50.7	14.4 yrs (widespread pain)	Beck Depression Inventory
Present study	58/29	All right-handed	42.1/42.2	12.8 yrs (regional or widespread pain)	DSM-IV criteria (MDD, dysthymia, and GAD)
Study	Magnet strength	Homogeneity correction?	Smoothing kernel (FWHM, mm)	Significance threshold, WB	Significance threshold, ROI
Kuchinad et al.	1.5 T	Yes	10	$p < .05$[b]	$p < .001$[c]
Schmidt-Wilcke et al.	1.5 T	Yes	10	$p < .05$[b]	$p < .05$[d]
Present study	3 T	Yes	10	$p < .05$[b]	$p < .001$[c] and $p < .05$[d]

Abbreviations: FM = fibromyalgia; HCs = healthy controls; DSM IV = Diagnostic and Statistical Manual of the American Psychiatric Association IV; MDD = major depressive disorder; GAD = general anxiety disorder; T = tesla; FWHM = full-width half-maximum; WB = whole-brain search; ROI = ROI-based search.
[a] Age was entered as a covariate in the model [12].
[b] Corrected for multiple comparisons.
[c] Uncorrected.
[d] Corrected for multiple comparisons and size of search volume.

Bonferroni-corrected $p < .05/3$ or .0167 was used as the threshold of significance. MNI coordinates for significant clusters were transformed into Talairach coordinates using a nonlinear transformation proposed by the Cognition and Brain Sciences unit of the Medical Research Council of the United Kingdom (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). Mean voxel values for any significant clusters, as well as for the entire smoothed gray matter image segment, were extracted from each subject for use in further analyses.

2.3. Continuous measures of pain and affective symptoms

2.3.1. Pain duration

We chose pain duration, rather than momentary pain level, as a representation of clinical pain in this study due to the highly fluctuating nature of momentary pain in FM [9], and the notion that long-term changes in brain structure would more likely be affected by the time since onset of pain, rather than the momentary magnitude of pain. Pain duration was defined as the number of years between onset of pain and MRI scan. Because FM patients usually present with a preceding history of chronic regional pain [5], onset of pain from regional pain conditions (such as tension headaches, temporomandibular joint disorder, irritable bowel syndrome, and low back pain) was used when reported.

2.3.2. Depressive symptoms

Depressive symptoms were rated using the Center for Epidemiological Studies-Depression Scale (CES-Depression [3]), a 20-item self-report inventory designed to assess depressive mood. Respondents were asked to indicate how frequently they experienced each of a set of symptoms during the past week, ranging from 0 (less than 1 day) to 3 (5–7 days). The total possible score, ranging from 0 to 60, reflects both the number of symptoms and the frequency of their occurrence. The CES-Depression scale was administered within one week of the MRI scan.

2.3.3. Anxiety

Trait anxiety was measured using the 10-item Trait Anxiety scale from the State-Trait Personality Inventory (STPI [21]). Scores range from 10 to 40, with higher value indicating higher anxiety symptoms. This subscale has strong evidence of concurrent validity with other validated measures of anxiety, and has shown good test–retest stability [20]. This inventory was administered prior to any study-specific therapeutic intervention.

2.4. Statistical analysis

Aside from statistical parametric mapping, all statistical analyses were performed using SPSS, version 14.0 (SPSS Inc., Chicago, IL). Variables were examined for normality, and means and standard errors of the mean were calculated separately for each group. Between-group differences were tested using a one-way ANOVA, with a significance threshold of $p < .05$. For any significant clusters, the standardized residuals from a linear regression between mean voxel value (dependent) and TIV (independent) were calculated. Nonparametric bivariate correlations between cluster-specific GMV and other variables were performed using these standardized residuals, and Spearman's correlation coefficients were calculated. A Bonferroni correction for multiple comparisons (four variables: cluster-specific GMV, pain duration, depressive symptoms, and trait anxiety) was used, requiring a p value of $< .05/4$ or .0125.

3. Results

3.1. Demographic and global morphometric comparisons

The FM+AD, FM−AD, and healthy control groups were closely matched with respect to age (mean age 41.7, 42.6, and 42.2, respectively; $p = .94$; Table 3), gender (all female), and handedness (all right handed). The three groups did not differ significantly with respect to TIV (1531, 1556, and 1521 ml; $p = .70$) or global GMV (617, 637, and 635 ml; $p = .30$). There was also no significant difference in pain duration between FM+AD and FM−AD groups ($p = .31$).

3.2. Voxel-wise group comparisons in GMV using one-way ANOVA

Using the whole-brain search approach, the main effect of group revealed no clusters of significantly different GMV among

Table 2
Regions of interest used in VBM studies of fibromyalgia patients vs. healthy controls, defined *a priori*.

Study	Regions of interest
Kuchinad et al.	Cingulate cortex (anterior, mid, and posterior), insular cortex, dorsolateral prefrontal cortex, medial prefrontal cortex, parahippocampal gyrus
Schmidt-Wilcke et al.	Striatum (lentiform and caudate nuclei), thalamus
Present study	All of the above

Table 3
Mean age and morphometric characteristics in FM subjects and age-matched healthy controls.[a]

	FM+AD (N = 29)	FM−AD (N = 29)	HC (N = 29)	p value
Age	41.7 ± 3.8	42.6 ± 3.7	42.2 ± 3.8	.94 (NS)
TIV (ml)	1531 ± 53	1556 ± 64	1521 ± 66	.70 (NS)
Global GMV (ml)	617 ± 20	637 ± 21	635 ± 20	.30 (NS)
Duration of pain (yrs)	12.0 ± 3.5	13.6 ± 2.9	–	.31 (NS)

Abbreviations: FM+AD = fibromyalgia subjects with affective disorder; FM−AD = fibromyalgia subjects without affective disorder; HCs = healthy controls; NS = not significant; TIV = total intracranial volume; GMV = gray matter volume.
[a] All values are presented as 95% confidence intervals.

the three groups, when correcting for multiple comparisons. The ROI-based search yielded a cluster in the ventral portion of the left anterior insula, in which the main effect of group on GMV was significant (xyz = {−28, 21, −9}; $F(2, 83) = 10.88$; p = .026 corrected; Table 4; Fig. 1). Post-hoc analysis revealed a significant difference between healthy controls and FM+AD (p = .0033 corrected), but no significant difference between healthy controls and FM−AD (p = .65 corrected), and no significant difference between FM+AD and FM−AD (p = .32 corrected; Table 4; Fig. 2).

3.3. Bivariate correlations with pain duration and affective symptoms

Mean voxel values from the left anterior insula cluster were extracted for all FM subjects and corrected for TIV. There was a significant negative correlation between mean GMV in the left anterior insula cluster and STPI-Trait Anxiety scores (rho = −.470, p = .0002; Fig. 3) within FM subjects. This correlation remained significant even when controlling for group (rho = −.345, p = .008). No significant correlations were found between cluster-specific GMV and pain duration or CES-Depression scores.

4. Discussion

This is the largest study to date investigating differences in GMV between FM patients and healthy controls. Our main finding is a reduction in GMV in the left anterior insula in FM patients with AD compared to healthy controls. However, when comparing FM patients without AD to healthy controls, this difference in GMV disappears. Furthermore, we found that GMV in this region is inversely correlated with trait anxiety. Thus, it appears that the finding of decreased GMV in the left anterior insula can be attributed to affective disturbance.

Table 4
Results of one-way ANOVA, showing significant main effect of group on GMV.

Search strategy	Region	MNI coordinates of peak			F	Contrast	p[a]
		x	y	z			
WB	No significant clusters found						
ROI	Left anterior insula	−28	21	−9	10.88	Omnibus	.026
						HC > FM+AD	.0033*
						HC > FM−AD	.65
						FM−AD > FM+AD	.32

Abbreviations: GMV = gray matter volume; MNI = Montreal Neurological Institute; WB = whole-brain search; ROI = region-of-interest search; HC = healthy controls; FM+AD = fibromyalgia patients with affective disorder; FM−AD = fibromyalgia patients without affective disorder.
[a] Corrected for small search volume and multiple voxel-wise comparisons using family-wise error.
* Significant after Bonferroni correction for post-hoc analysis.

Previous research has shown the anterior insula to be involved in processing a wide variety of interoceptive stimuli (including pain, heartbeat awareness, thirst, coolness, warmth, gut and bladder distension), and a similarly wide range of emotional feelings (including anger, fear, sadness, disgust, unfairness, maternal and romantic love, happiness, sexual arousal, trust, and sculptural beauty) [7]. Our finding of an inverse relationship between anterior insula GMV and trait anxiety thus appears to be consistent with "burnout" due to overutilization of the emotional-processing function of this region. However, one can also argue that this finding is consistent with atrophy due to under-utilization of positive affective states, especially given evidence that positive emotional processing is lateralized to the left forebrain [7,22].

Despite our somewhat large sample size, we were unable to replicate the previously reported findings of a global GMV difference between patients and controls [12]. We were also unable to replicate differences in regional GMV in most previously reported ROIs (left parahippocampal gyrus, left and right mid/posterior cingulate, medial frontal cortex [12]; bilateral striatum, and left thalamus [18]). There are several potential reasons for the discrepancies between our present findings and previously published studies. One explanation may be that our patient population has less severe disease on average, compared to those enrolled in the previous studies. Indeed, the mean age of our FM subjects is a decade younger than the mean ages of the FM subjects in the previous studies (Table 1). However, the mean duration of pain, which we defined as time since onset of continuous chronic regional or widespread pain, is comparable to that reported in previous studies. Nevertheless, we cannot rule out a synergistic interaction between age and disease duration which may explain the previously published differences in regional GMV that were not replicated in the present study.

Another potential reason for our inability to replicate most of these previously reported GMV differences between patients and controls is the manner in which we controlled for affective disorder. Unlike Kuchinad et al., we considered the presence of dysthymia and general anxiety disorder, in addition to major depressive disorder, as potential confounders in the relationship between FM diagnosis and changes in GMV. While controlling only for major depressive disorder, Kuchinad et al. still found a reduction in left insula regional GMV in FM patients compared to controls. However, while controlling not only for major depressive disorder in our study, but also for dysthymia and general anxiety disorder, we found no difference in left insula GMV between FM patients and healthy controls. Our finding of a significant relationship between trait anxiety and left insula GMV further underscores the importance of controlling for other types of affective disorders when comparing FM patients to controls.

A final explanation for our inability to replicate most of the previous findings, is that our VBM protocol may have had a lower signal-to-noise ratio than the methods used in the previous studies. For example, our voxel dimensions (.9375 × .9375 × 1.5 mm) were slightly larger than those reported by Schmidt-Wilcke et al. (1 × 1 × 1.08 mm), and may have contributed to slightly decreased accuracy in gray matter segmentation. However, our voxel dimensions were still within the maximum voxel size suggested by the accepted VBM guidelines [2]. Regarding our segmentation, normalization, and modulation algorithm, several other studies have used the same VBM5 toolbox and were able to detect significant GMV changes in illnesses such as major depression [8], bipolar disorder [13], and Alzheimer's dementia [10], and also changes in normal childhood development [4]. While these studies are not a substitute for formal testing and comparison of methods, they do provide some evidence of the sensitivity of the VBM5 toolbox in detecting differences in GMV between clinical populations and controls.

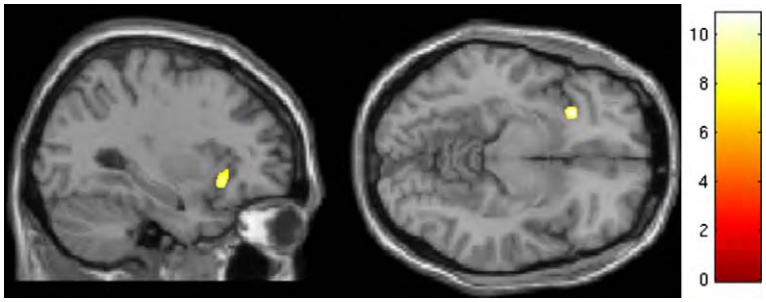


Fig. 1. Cluster showing significant main effect of group on gray matter volume, using region-of-interest search, located within the left anterior insula. Color scale is for *F* statistic.

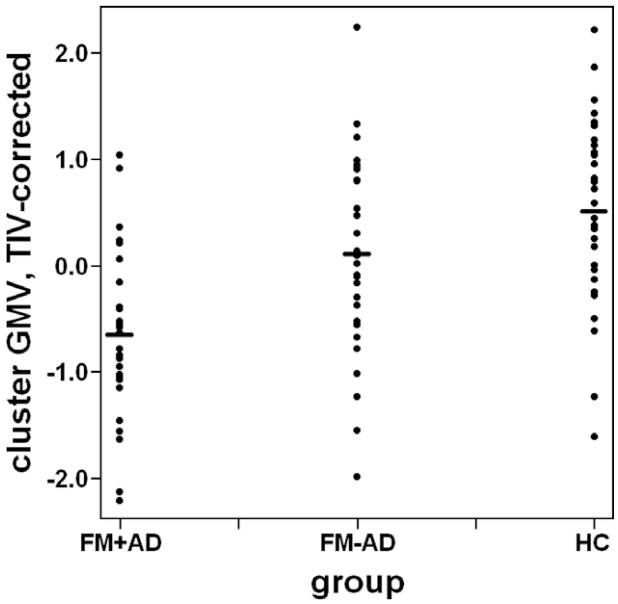


Fig. 2. Scatter plot of gray matter volume (GMV) within the left anterior insula cluster, corrected for total intracranial volume (TIV), by group. *Abbreviations:* FM+AD = fibromyalgia subjects with affective disorder; FM−AD = fibromyalgia subjects without affective disorder; HCs = healthy controls.

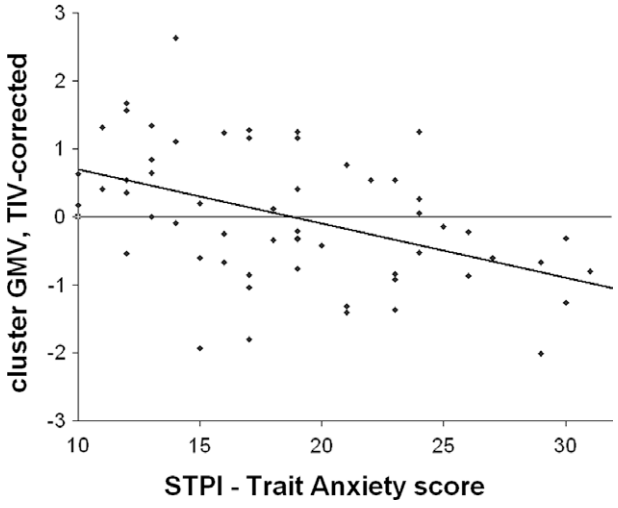


Fig. 3. Significant negative correlation between gray matter volume (GMV) in the left anterior insula cluster corrected for total intracranial volume (TIV), and trait anxiety scores, within FM patients. *Abbreviations:* STPI = State-Trait Personality Inventory.

There are several potential limitations to the interpretation of the present findings. First, aside from potential differences in clinical severity as mentioned above, the populations from which we drew our sample groups inevitably differ from the populations sampled in the previously published studies, in ways that may have altered our ability to detect differences in global or regional GMV. For example, our sample of healthy controls may have had a distribution of cognitive aptitude worse than the controls used in the previous studies, thus biasing our results towards the null. Secondly, the retrospective nature of this study prohibits any conclusion regarding a causal relationship between affective disorder in FM and decreased regional GMV. Furthermore, due to the occasional presence of susceptibility artifacts in the base of the brain in our sample, we excluded all voxels inferior to $z = -22$, and therefore could not assess for possible differences in regional GMV in the amygdala, brainstem, or cerebellum. Finally, given that our study sample was limited to right-handed women, our findings may not be generalizable to men or to left-handed individuals.

In conclusion, we found a reduction in gray matter volume in the left anterior insula in FM patients with affective disorder compared to healthy controls, and this difference in GMV appears to be attributable to affective disturbance. Despite a somewhat larger sample size, our study did not replicate the previous reports of other regional and global GMV differences between patients and controls, perhaps due to our use of a younger sample population and a broader definition of affective disorder. We recommend that future investigations using VBM in chronic pain populations should control for all these factors when making group-level comparisons.

Acknowledgments

We acknowledge Rupal Patel, Linda Skalski, Laura Mayo-Bond, Emily Thorpe, and Rosie Iordanova for their invaluable assistance with data acquisition and management. Our research was supported in part by the National Institutes of Health (NIH T-32 HD007422-17, 5-R01-AR050044, and K01 AT01111-01), Department of Defense (DAMD 17-00-2-0018, W81XWH-07-2-0050), and University of Michigan General Clinical Research Center (National Center for Research Resources, UL1RR024986). There are no conflicts of interest regarding this study, for any of the authors.

References

[1] Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, Gitelman DR. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci 2004;24:10410–5.
[2] Ashburner J, Friston KJ. Voxel-based morphometry – the methods. Neuroimage 2000;11:805–21.
[3] Barlow JH, Wright CC. Dimensions of the Center of Epidemiological Studies-Depression Scale for people with arthritis from the UK. Psychol Rep 1998;83:915–9.
[4] Baumgartner T, Speck D, Wettstein D, Masnari O, Beeli G, Jäncke L. Feeling present in arousing virtual reality worlds: prefrontal brain regions

differentially orchestrate presence experience in adults and children. Front Hum Neurosci 2008;2:8.
[5] Bergman S, Herrstrom P, Jacobsson LT, Petersson IF. Chronic widespread pain: a three year followup of pain distribution and risk factors. J Rheumatol 2002;29:818–25.
[6] Brett M, Anton JL, Valabregue R, Poline JB. Region of interest analysis using an SPM toolbox [abstract]. Neuroimage 2002;16:S497.
[7] Craig AD. How do you feel – now? The anterior insula and human awareness. Nat Rev Neurosci 2009;10:59–70.
[8] Frodl T, Koutsouleris N, Bottlender R, Born C, Jäger M, Mörgenthaler M, Scheuerecker J, Zill P, Baghai T, Schüle C, Rupprecht R, Bondy B, Reiser M, Möller HJ, Meisenzahl EM. Reduced gray matter brain volumes are associated with variants of the serotonin transporter gene in major depression. Mol Psychiatry, published online 1 July 2008.
[9] Harris RE, Williams DA, McLean SA, Sen A, Hufford M, Gendreau RM, Gracely RH, Clauw DJ. Characterization and consequences of pain variability in individuals with fibromyalgia. Arthritis Rheum 2005;52:3670–4.
[10] Honea RA, Thomas G, Harsha A, Cronk B, Donnelly J, Brooks WM, Burns JM. O1-02-02: physical fitness is associated with preservation of brain volume in Alzheimer's disease. Alzheimers Dement 2008;4:T109.
[11] Kato K, Sullivan PF, Evengård B, Pedersen NL. Chronic widespread pain and its comorbidities: a population-based study. Arch Intern Med 2006;166:1649–54.
[12] Kuchinad A, Schweinhardt P, Seminowicz DA, Wood PB, Chizh BA, Bushnell MC. Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? J Neurosci 2007;27:4004–7.
[13] Ladouceur CD, Almeida JR, Birmaher B, Axelson DA, Nau S, Kalas C, Monk K, Kupfer DJ, Phillips ML. Subcortical gray matter volume abnormalities in healthy bipolar offspring: potential neuroanatomical risk marker for bipolar disorder? J Am Acad Child Adolesc Psychiatry 2008;47:532–9.
[14] Lindell L, Bergman S, Petersson IF, Jacobsson LT, Herrström P. Prevalence of fibromyalgia and chronic widespread pain. Scand J Prim Health Care 2000;18:149–53.
[15] Mease P, Arnold LM, Bennett R, Boonen A, Buskila D, Carville S, Chappell A, Choy E, Clauw D, Dadabhoy D, Gendreau M, Goldenberg D, Littlejohn G, Martin S, Perera P, Russell IJ, Simon L, Spaeth M, Williams D, Crofford L. Fibromyalgia syndrome. J Rheumatol 2007;34:1415–25.
[16] Schmidt-Wilcke T, Leinisch E, Gänssbauer S, Draganski B, Bogdahn U, Altmeppen J, May A. Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients. Pain 2006;125:89–97.
[17] Schmidt-Wilcke T, Leinisch E, Straube A, Kämpfe N, Draganski B, Diener HC, Bogdahn U, May A. Gray matter decrease in patients with chronic tension type headache. Neurology 2005;65:1483–6.
[18] Schmidt-Wilcke T, Luerding R, Weigand T, Jürgens T, Schuierer G, Leinisch E, Bogdahn U. Striatal grey matter increase in patients suffering from fibromyalgia – a voxel-based morphometry study. Pain 2007;132:S109–16.
[19] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:22–3.
[20] Spielberger CD. Manual for the State-Trait Anxiety Inventory (STAI) (self-evaluation questionnaire). Palo Alto (CA): Consulting Psychologists Press; 1979.
[21] Spielberger CD. Preliminary manual for the State-Trait Personality Inventory. Tampa (FL): Human Resources Institute, University of South Florida; 1979.
[22] Tucker DM. Lateral brain function, emotion, and conceptualization. Psychol Bull 1981;89:19–46.
[23] Valfrè W, Rainero I, Bergui M, Pinessi L. Voxel-based morphometry reveals gray matter abnormalities in migraine. Headache 2008;48:109–17.
[24] White KP, Speechley M, Harth M, Ostbye T. The London Fibromyalgia Epidemiology Study: the prevalence of fibromyalgia syndrome in London, Ontario. J Rheumatol 1999;26:1570–6.
[25] Williams DA, Gracely RH. Biology and therapy of fibromyalgia. Functional magnetic resonance imaging findings in fibromyalgia. Arthritis Res Ther 2006;8:224.
[26] Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA, Reynolds WJ, Romano TJ, Russell IJ, Sheon RP. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160–72.

Review

Biology and therapy of fibromyalgia

Functional magnetic resonance imaging findings in fibromyalgia

David A Williams[1,2] and Richard H Gracely[1,3]

[1]Chronic Pain and Fatigue Research Center, Department of Internal Medicine, Division of Rheumatology, University of Michigan Health System, University of Michigan, Ann Arbor, MI, USA
[2]Department of Psychiatry, University of Michigan Health System, University of Michigan, Ann Arbor, MI, USA
[3]Department of Neurology, University of Michigan Health System, University of Michigan and Ann Arbor VAMC, Ann Arbor, MI, USA

Corresponding author: Richard H Gracely, rgracely@med.umich.edu

Published: 17 January 2007
This article is online at http://arthritis-research.com/content/8/6/224

Arthritis Research & Therapy 2006, **8:**224 (doi:10.1186/ar2094)

Abstract

Techniques in neuroimaging such as functional magnetic resonance imaging (fMRI) have helped to provide insights into the role of supraspinal mechanisms in pain perception. This review focuses on studies that have applied fMRI in an attempt to gain a better understanding of the mechanisms involved in the processing of pain associated with fibromyalgia. This article provides an overview of the nociceptive system as it functions normally, reviews functional brain imaging methods, and integrates the existing literature utilizing fMRI to study central pain mechanisms in fibromyalgia.

Introduction

Fibromyalgia (FM) affects six to ten million Americans, [1] and the incidence is estimated to be one to four percent in the general population [2]. The symptoms associated with FM significantly affect patients' quality of life [3] and can lead to extensive use of health care services [4]. Fibromyalgia is experienced as a chronic, widespread pain condition accompanied by fatigue, tenderness, sleep disturbance, decrements in physical functioning, and disruptions in psychological functioning (for example, memory problems, diminished mental clarity, mood disturbances, and lack of well-being) [5,6]. To date, a precise cause of FM is unknown.

The diagnostic criteria for FM are, in part, based upon a demonstration of tenderness in 11 of 18 defined muscular sites [7]. Recent evidence, however, suggests the tenderness is not confined to these sites in FM, but can be observed throughout the body, including non-muscular sites such as the thumb [8]. The general and widespread nature of pain in fibromyalgia strongly suggests the involvement of central mechanisms that facilitate bodily spontaneous pain and that increase sensitivity to painful blunt pressure. These central mechanisms may involve spinal or supraspinal modulation of normal peripheral input, or efferent mechanisms that alter pain sensitivity at the periphery. These underlying central mechanisms of FM are likely to be reflected in altered supraspinal processing and may originate, in part, at supraspinal sites.

The ability to evaluate human supraspinal processing has been enhanced greatly by major advances in brain imaging techniques. These methods vary in invasiveness, and in temporal and spatial resolution. These procedures evaluate neural activity from cerebral blood flow or glucose metabolism, neurochemistry from resonance spectroscopy techniques, changes in the volume of anatomical structures, and the amount of receptor binding by specific ligands. The focus of this paper is to describe the recent use of functional brain imaging techniques in studies of FM. It begins with a description of the nociceptive system as it functions normally, follows with an overview of functional brain imaging methods, and concludes with a synopsis of functional magnetic resonance imaging (fMRI) findings, shedding light on aberrant central mechanisms responsible for the pain of FM.

The nociceptive system

The nociceptive system is a warning system of actual or imminent damage to the body. It is a self-contained sensory system composed of peripheral sensory fibers (primary afferents) connected to multiple spinal tracts and brain regions. Normally, relatively intense noxious stimuli are required to activate this system, a feature most likely associated with promoting, rather than hindering, adaptive behavior.

ACC = anterior cingulate cortex; BOLD = blood oxygen level dependent; FM = fibromyalgia; fMRI = functional magnetic resonance imaging; IC = insular cortex; PET = positron emission tomography; PFC = prefrontal cortex; rCBF = regional cerebral blood flow; SI = primary somatosensory cortex; SII = secondary somatosensory cortex; SPECT = single photon emission computed tomography.

Peripheral nociceptors

Sensory fibers modulating pain sensations innervate all body tissues in order to respond to the most compelling dangers (for example, heat, cold, mechanical pressure, chemical, and metabolic stimuli such as low pH). These sensory fibers are composed of two types: thinly myelinated Aδ fibers and unmyelinated C fibers. Aδ fibers are rapidly conducting and transmit signals that produce perceptions of relatively sharp, incapacitating pain. Aδ pain has been referred to as 'first pain', consistent with its ability to rapidly warn and motivate avoidance of tissue-damaging stimuli. In contrast, C fiber afferents conduct more slowly and tend to produce perceptions of aching or burning pain referred to as 'second pain'. Second pain is diffuse, prolonged and aversive, and is the main component of pain associated with chronic medical conditions [9].

Spinal cord secondary projections

Nociceptor afferents enter the spinal cord via the dorsal roots and terminate in lamina I, II, and V of the superficial dorsal horn. Activity in these nociceptors releases excitatory neurotransmitters at their terminals that activate secondary projection neurons. Excitatory transmitters include glutamate, which activates post-synaptic N-methyl-D-aspartate receptors, Substance P, and neurokinin A, which in turn activate post-synaptic neurokinin A receptors.

Neurons in lamina I and II respond to specific noxious stimuli within small receptive fields (for example, in muscle or joint). These second order neurons are termed 'nociceptive-specific' and are dominated by Aδ fiber input. Nociceptive neurons in lamina V respond to both noxious and non-noxious mechanical stimuli and are termed 'wide dynamic range' neurons.

Ascending pathways and brain networks

The secondary neurons originating within the dorsal horn ascend in three primary contralateral tracts projecting to the thalamus and reticular formation. The largest tract is the spinothalamic tract, providing nociceptive information to thalamic nuclei [10] as well as to the primary (SI) and secondary (SII) somatosensory cortices. SI and SII are cortical regions believed to be involved in sensory-discriminative aspects of pain as well as in the anticipation of painful stimuli [11]. Spinothalamic tract projections also facilitate nociceptive input to the insular cortex (IC), which has interconnections with the amygdala, prefrontal cortex (PFC), and anterior cingulate cortex (ACC). These regions form a network involved in affective, cognitive, and autonomic responses to nociception. Two of these regions (IC and PFC cortices) may also integrate nociceptive signals with memory of previous events, thus providing meaning and the identification of potential threats associated with painful stimuli [12,13]. In addition to the spinothalamic tract, there are at least two other prominent ascending pathways from the spinal cord to the brain [14-17]. Like aspects of the spinothalamic tract, both of these pathways are thought to mediate the interactions between nociceptive signals, cognition, and emotional responses.

Consistent with the above, a meta-analytic review of acute pain neuroimaging studies suggested that the six most commonly activated brain regions for pain in healthy subjects were SI, SII, IC, ACC, PFC and thalamus [18]. Interestingly, simply the anticipation of pain activates similar regions (PFC, anterior insula, ACC). These regions are involved in the formation of cognitive and affective representations of pain involving memories of past events and understandings of the present and future implications of events signaled by pain [19]. Chronic pain states on the other hand have been more difficult to study; but summary impressions suggest that relative to acute pain processing, chronic pain processing reflects decreased sensory processing (for example, SI, SII) in favor of enhanced activation of regions associated with cognitive, emotional, and introspective processing of events [18].

Neuroimaging: a summary of methods

Several neuroimaging methodologies exist, each providing a slightly different temporal window for understanding the central processing of pain. The assessment of temporal characteristics is best performed through the use of the electroencephalogram or with the more advanced application of magnetoencephalography, which offers the ability to record the timing of brain events on the order of milliseconds. These methods are best used with stimuli having temporally precise onsets, such as provided by electrical, laser and acoustic sources, or by well controlled mechanical stimulation. These methods have not been very useful for stimuli that do not have such characteristics, such as the blunt pressure used in the assessment of tenderness in FM. While good for assessing temporal characteristics, the spatial resolution of these methods is relatively poor in comparison to other methods and is aided by the use of the modalities described below.

Assessment of spatial characteristics often uses methods that do not measure neural activity directly but, instead, use specialized equipment to infer neural activity from highly localized increases in regional cerebral blood flow (rCBF) occurring in response to anticipated neural metabolic demand. The local increase in rCBF can be imaged by infusion of radioactive tracers with methods such as single photon emission computed tomography (SPECT) or positron emission tomography (PET). In the case of fMRI, the different magnetic properties of oxygenated and deoxygenated blood serve as an intrinsic tracer (that is, the blood oxygen level dependent (BOLD) fMRI signal).

The various imaging methods differ in the ability to assess baseline rCBF, and in temporal and spatial resolution. One advantage of the early methods of SPECT and PET is that they could assess static rCBF; for example, comparing the

baseline neural activity among different patient populations. Relative disadvantages were the need to infuse radioactive tracers, and modest temporal and spatial resolution. The time needed for a single image of the entire brain was approximately 30 minutes with SPECT, 1 minute with PET, and 2 seconds with fMRI. Localization also improves accordingly; fMRI methods now allow visualization of activity in discrete regions, such as thalamic nuclei, with resolutions as small as 1 to 2 mm. A potential disadvantage of the fMRI BOLD, however, is that such designs must repeatedly switch between stimulus 'on' and 'off' conditions, making imaging of static or long-lasting drug effects (for example, before and after treatment) more difficult.

Evaluation of pain processing in fibromyalgia

Early SPECT studies

The pioneering application of brain functional imaging to patients with FM used the SPECT method. Mountz [20] used SPECT to evaluate baseline levels of rCBF in ten patients with fibromyalgia and in seven healthy control subjects. In this initial study, patients received infusions of approximately 25 mCi of ^{99m}Tc-HMPAO, a radioactive tracer that facilitated the imaging of rCBF. After the infusion, the subjects underwent a 32 minute SPECT scan. This method resulted in a semi-quantitative measure of rCBF with a resolution of about 8.5 mm. The analysis examined overall activity in large regions of interest corresponding to the right and left thalamus and the right and left head of the caudate nucleus. Results from this early study suggested that patients with FM had lower rCBF (that is, lower neural activity) than healthy control subjects during a quiescent resting state. Reduced neural activity was found both in the right and left thalamus and in the right and left caudate nucleus.

Another group followed this initial investigation with a similar study. Kwiatek [21] used SPECT to assess resting rCBF in 17 patients with FM and in 22 healthy control subjects. These investigators observed decreased rCBF in the right thalamus, the inferior pontine tegementum and near the right lentiform nucleus but, unlike the initial study, no decreases in either the left thalamus or in the caudate nuclei were noted.

The consistent finding of reduced rCBF in the right thalamus was also observed in a second study by the Mountz group [22], who examined the influence of historical factors on the SPECT results. These authors divided the sample of patients with fibromyalgia into those with a traumatic etiology ($n = 11$) and those with a more gradual onset ($n = 21$). Both patient groups, compared to 29 healthy controls, showed significantly decreased rCBF in the left and right thalamus. However, only patients with a gradual atraumatic etiology showed reduced rCBF in the left and right caudate.

The findings of decreased rCBF in the thalamus and in the caudate nucleus are not unique to FM. Low rCBF has been observed in patients with pain due to traumatic peripheral neuropathy [23] and to metastatic breast cancer [24]. Abnormally low rCBF levels in the caudate nucleus have been documented in patients with pain related to spinal cord injury [25], and in restless leg syndrome [26]. The caudate nucleus receives a large nociceptive input from spinal pain pathways, including both nociceptive-specific neurons that signal the presence of pain, and wide-dynamic-range neurons that provide graded responses throughout the range of innocuous and painful stimulation [27-29].

The caudate nucleus may also be involved in intrinsic analgesia systems [30,31]. Although the cause of thalamic and caudate decreases in rCBF is unknown, inhibition of activity in these regions is associated with, and may result from, prolonged excitatory nociceptive input [23]. The present findings of lowered resting rCBF in these structures in FM patients are consistent with a mechanism of tonic inhibition maintained by persistent excitatory input associated with ongoing and spontaneous pain. That is, the widespread pain in FM is sufficient to activate pain inhibitory mechanisms, and one consequence of this inhibition is reduced resting and evoked activity in the thalamus.

Methodological considerations for using the improved spatial resolution of fMRI

Before fMRI could be used to explore underlying pain mechanisms in FM, several methodological hurdles needed to be resolved. Unlike acute or surgical pain, where the nature and timing of the pain stimulus can be controlled, imaging FM pain is more challenging given that neither the experimenter nor the patient has the ability to systematically manipulate the characteristics of the condition [18]. Thus, methodological advances for delivering and removing a standardized pain stimulus needed to be made that would permit: the rapid onset and off-set of the evoked-pain stimuli; the delivery of stimuli that were relatively unbiased by psychosocial factors; and the use of a pain stimulus that was meaningful and relevant to the condition of FM.

Many studies of FM pain apply pressure to specific FM tender points. This is commonly done using 'ascending' testing methods, such as tender point counts or dolorimetry, where each subsequent stimulus is predictable in its intensity. These methods are easy to apply clinically, but can be influenced by response biases originating from both the subject and examiner. Improved methods that present stimuli in a random, unpredictable fashion (for example, Multiple Random Staircase) tend to minimize the influence of these factors [32].

fMRI studies have the added methodological hurdle of needing to apply standardized pressure to regions of the body accessible during scanning and with methods that can be accommodated within the scanning environment. Thus, methods were devised that applied blunt pressure (1 cm diameter hard rubber probe) to the thumbnail. This site was

chosen for the dense innervation of the thumb, and the large representation of the thumb in the primary somatosensory cortex. In addition, this site implicitly acknowledges that the tenderness observed in FM is not confined to classic tender points; tenderpoints, rather, are regions in which everyone is more tender and are thus more convenient for manual testing. The use of the thumb also implicitly implies that the tenderness observed in FM is neither due to muscle sensitivity nor confined to muscles but, rather, is a property of deep tissue, with the tenderness of FM being generally expressed over the entire body.

Another extremely important methodological consideration addressed the fact that patients and controls differed not only with respect to the presence of clinical pain but also to the fact that the presence of concomitant clinical pain could alter their perception of the evoked pain stimuli. Thus, responses to stimuli needed to be evaluated in the context of equal stimulus intensities for patients and controls and under conditions of equal perceptual intensities. This approach permitted comparisons of neural activations between FM patients and normal controls associated with pain processing when either perceived pain intensity or stimulus intensities were constant.

Central pain augmentation in fibromyalgia

Using pressure-based Multiple Random Staircase to equate evoked pain perception between patients and normal controls, one of the first fMRI studies of FM applied blunt pressure to the left thumbnail bed of 16 right-handed patients with FM and 16 right-handed matched controls [33]. Each FM patient underwent fMRI while moderately painful pressure was being applied. The functional activation patterns in FM patients were compared with patterns in normal controls. The results show that equal perceived pain intensity (achieved with significantly less pressure in the patients than controls), produced similar increases in neural activity in a network of brain structures implicated in pain processing (Figure 1). These increases were observed in structures involved in sensory discriminative processing (contralateral SI, SII), sensory association (contralateral superior temporal gyrus, inferior parietal lobule), motor responses (contralateral putamen and ipsilateral cerebellum) and affective processing (contralateral insula). Patients and controls also shared a similar region of decreased neural activation in the ipsilateral SI.

In contrast to the extensive common activations observed in both patients and controls when subjective pain perception was equated, there were no common activations when the actual pressure stimulus intensity was equated. Applying a low stimulus pressure to both healthy controls and FM patients resulted in 13 regions showing statistically greater activation for patients (that is, contralateral SI, inferior parietal lobule, insula, ACC and posterior cingulate cortex; ipsilateral SII cortex; bilateral superior temporal gyrus, and cerebellum) whereas only one region (ipsilateral medial frontal gyrus) demonstrated greater activation in controls.

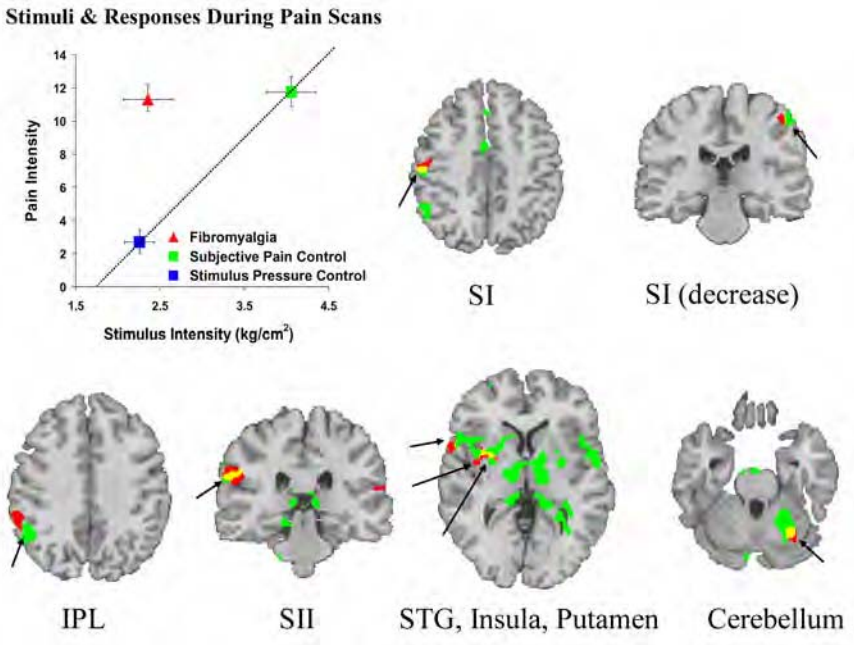
These findings suggest that the greater perceived intensity of standardized low pressure stimuli by persons with FM is consistent with a model of centrally augmented pain processing. These results also suggest that the brain activations in patients and controls are consistent with their verbal reports of pain magnitude. In addition, these results demonstrate that, in the caudate nucleus and the thalamus, patients with FM showed reduced activation in comparison to controls. This lack of response is, at first glance, consistent with the finding of reduced basal activity in these structures [20-22]. However, it is important to note that the finding of basal levels could indicate either lack of evoked pain responsivity (inhibited system) or be responsible for increased pain sensitivity (greater response range; that is, activity can increase further before encountering a physiological 'ceiling'). Thus, this apparently consistent result is not necessarily expected and the implications of these results will depend on the results of further studies [33].

The findings of the Gracely and colleagues [33] study have been supported by a second study using a contact heat stimulus. Cook and colleagues [34] showed that perceptually matched heat pain stimuli (that is, matched subjective perceptual pain ratings) applied to the left hand (evoked by less heat in patients (mean 47.4°C) versus controls (48.3°C)) resulted in similar brain activation patterns between a group of 9 female FM patients and 9 female healthy controls. In contrast, when evoked-pain stimuli were matched on actual stimulus intensity (that is, temperature), significantly greater activations in contralateral IC were seen in FM patients. In addition, these authors compared responses to non-painful heat stimuli, and observed that random warm stimuli between 34°C and 42°C evoked significantly greater activity in FM patients in bilateral PFC, supplemental motor areas, and in contralateral ACC.

Mechanisms of hyperalgesia in fibromyalgia

Hyperalgesia refers to a condition where normally noxious stimuli produce an exaggerated or prolonged pain response. In an attempt to image a hyperalgesic response to evoked pain, Grant and colleagues [35] used fMRI to compare the effects of multiple stimulus pressures delivered to the left thumb of 13 FM patients and 13 control subjects. During scanning, the subjects received 25 seconds of no pressure alternating with 25 seconds of pressure stimuli adjusted for each subject to produce: a non-painful touch sensation; painful pressure sensations rated as 'faint'; sensations rated as 'very mild'; and sensations rated between 'moderate' and 'slightly intense' pain. In each scan the subjects received each of the four stimulus pressures three times in a random sequence. Similar to the study described above [33], the amount of stimulus pressure needed to evoke the various subjective levels of pain was significantly lower in the patients; however, both patients and controls showed graded responses to stimulus pressure in regions involved in processing the sensory discriminative dimension of pain

Figure 1



Functional magnetic resonance imaging (fMRI) responses to painful pressure applied to the left thumb in patients with fibromyalgia and healthy control subjects. The top left graph shows mean pain rating plotted against stimulus intensity for the experimental conditions. In the 'patient' condition, a relatively low stimulus pressure (2.4 kg/cm^2) produced a high pain level (11.30 ± 0.90), shown by the red triangle. In the 'stimulus pressure control' condition, shown by the blue square, administration of a similar stimulus pressure (2.33 kg/cm^2) to control subjects produced a very low level of rated pain (3.05 ± 0.85). In the 'subjective pain control' condition, shown by the green square, administration of significantly greater stimulus pressures to the control subjects (4.16 kg/cm^2) produced levels of pain (11.95 ± 0.94) similar to the levels produced in patients by lower stimulus pressures. The remainder of the figure shows common regions of activation in patients (red) and in the 'subjective pain control' condition (green), in which the effects of pressure applied to the left thumb sufficient to evoke a pain rating of 11 (moderate) is compared to the effects of innocuous pressure. Significant increases in the fMRI signal resulting from increases in regional cerebral blood flow are shown in standard space superimposed on an anatomical image of a standard brain (MEDx, Medical Numerics, Inc. 20410 Observation Drive, Suite 210, Germantown, Maryland 20876 USA). Images are shown in radiological view with the right brain shown on the left. Overlapping activations are shown by yellow. The similar pain intensities, produced by significantly less pressure in the patients, resulted in overlapping or adjacent activations in contralateral primary somatosensory cortex (SI), inferior parietal lobule (IPL), secondary somatosensory cortex (SII), superior temporal gyrus (STG), insula, putamen, and in ipsilateral cerebellum. The fMRI signal was significantly decreased in a common region in ipsilateral SI. Modified from Gracely and colleagues [33].

sensation, including contralateral (right) thalamus, SI and SII. Control subjects showed graded responses in right insula and anterior cingulate that were not found in the patients. These results indicate common sensory discriminative functions in both groups that occur with lower objective stimulus intensities for FM patients. The reduced affective response (that is, no activation in ACC or insula in FM patients) suggests that FM patients may not find the evoked pain stimulus affectively arousing due, possibly, to affective adaptation associated with their prolonged pain.

Affective modulation of pain in fibromyalgia

Depressed mood often accompanies chronic pain, but depressed mood may not augment the sensory aspects of pain. Instead, mood may exert its own independent influence on pain processing. Giesecke and colleagues [36] conducted a study that evaluated the effect of symptoms of depression and/or clinically diagnosed major depressive disorder on pain processing in patients with FM. In this study, 30 patients with FM received fMRI scans during administration of painful blunt pressure to the left hand matched for equally perceived painful pressure. Symptoms of depression were measured with the Center for Epidemiological Studies Depression Scale (CES-D). Neither the extent of depression nor the presence of comorbid major depression modulated the sensory-discriminative aspects of pain processing (that is, localized imaging of sensory pain and reporting its level of intensity). However, symptoms of depression and the presence of major depressive disorder were associated with the magnitude of evoked-pain neuronal activations in brain regions associated with affective-motivational pain processing (that is, the bilateral amygdalae and contralateral anterior insula). These data suggest that there are parallel, somewhat independent neural pain-processing networks for sensory and affective pain elements. The implication for treatment is that addressing an individual's depression (for example, by

prescribing an antidepressant medication that has no analgesic properties) will not necessarily have an impact on the sensory dimension of pain.

Cognitive modulation of pain in fibromyalgia

Locus of control

Locus of control for pain refers to patients' perceptions about their personal ability to control pain. In studies of patients with chronic rheumatological pain conditions, a stronger belief in internal locus of control for pain has been associated with lower levels of physical and psychological symptoms, and better response to therapy [37-45]. In studies of patients with FM, internal locus of control has been associated with better affect, reduced symptom severity, and less disability in upper and lower extremity function [46] and generally improved levels of functional status [47]. Most patients with FM, however, are more external in their locus of control compared to other rheumatological conditions or patients with chronic pain generally [46,48,49]. Several of these studies have concluded that increasing internal locus of control in patients with FM should increase the likelihood of improving function and decreasing impairment (for example, McCarberg and colleagues [47]). In a study designed to explore the neural substrates of locus of control, a sample of 20 females and 1 male meeting American College of Rheumatology criteria for FM were selected [50]. Each patient received fMRI scans during administration of painful blunt pressure to the left hand matched for equally perceived painful pressure. Locus of pain control was assessed using the Beliefs in Pain Control Questionnaire [51]. Results of this study found that stronger beliefs in an internal locus of control were significantly correlated with neuronal activations in the contralateral SII ($r = 0.84$, $p < 0.05$) in response to evoked pain. These results support the hypothesis that greater levels of internal locus of control are associated with greater magnitude of neuronal activation in this region associated with sensory discrimination and pain intensity encoding.

Catastrophizing

Another common cognitive factor known to modulate pain reports is catastrophizing, an attributional style/behavior in which pain is characterized as awful, horrible and unbearable. Catastrophizing appears to play a substantial role in the development of pain chronicity. Burton and colleagues [52] found that catastrophizing accounted for over half (57%) of the variance in predicting the onset of a chronic pain condition from an acute pain event. Catastrophizing was once thought to be a symptom of depression but is now recognized as an independent factor that is only partially associated with depression. Catastrophizing has been suggested to augment pain perception via enhanced attention to painful stimuli and through heightened emotional responses to pain. This study hypothesized that catastrophizing would, therefore, influence activation of neural structures implicated in pain processing. Blunt pressure pain was applied to 29 FM patients while controlling for depression statistically. Independent of depression, catastrophizing modulated evoked-pain activity in a number of brain structures related to the anticipation of pain (contralateral medial frontal cortex, ipsilateral cerebellum), attention to pain (contralateral anterior cingulate gyrus, bilateral dorsolateral prefrontal cortex), and to both emotional (ipsilateral claustrum, interconnected to the amygdala) and motor (contralateral lentiform nuclei) responses [53]. These findings suggest that pain catastrophizing exerts influence on pain processing that is independent of the influence of depression and supports the hypothesis that catastrophizing influences pain perception through altering attention and anticipation, and heightening emotional responses to pain. Like locus of control, therapies targeting the modification of catastrophizing might be useful in preventing the transition from acute to chronic pain in susceptible individuals.

Fibro-fog

While cognition appears to modulate the experience of pain, it is also likely that pain interferes with the ability to think and process information. A well-known complaint of patients with FM is that of an overall impaired cognitive state that has been referred to as 'fibro fog'.

The cognitive deficits observed in FM resemble those found in aging. For example, patients with FM tend to complete measures of working memory with a proficiency that is similar to healthy controls who are 20 years older [54,55]. Neuroimaging studies of working memory in aged populations suggest that older subjects can show levels of performance that approach the levels of younger control subjects but must use relatively more cognitive resources. Bangert and colleagues [55] used fMRI to assess brain activity during a working memory task in 12 FM patients and 9 age and education-matched control subjects. The results show that both FM patients and healthy controls were able to achieve similar performances on the tasks. The imaging results, however, revealed that, in order to achieve this similar level of performance, FM patients needed to use far greater brain resources. FM patients showed more extensive neural activation in frontal and parietal regions, including bilateral activation in the middle frontal gyrus and right-side activation in medial frontal gyrus, superior parietal lobe, and precentral gyrus. These results support the hypothesis that FM patients show an aging effect that is using increasing cognitive resources to maintain comparable levels of performance as their same-aged peers.

Conclusions and future directions

At the present time, functional brain imaging in FM has revealed the following insights. First, FM patients differ from healthy controls in baseline levels of neural activity, specifically in the caudate nucleus. Second, administration of a noxious pressure or heat stimulus results in changes in brain activity consistent with the verbal reports of patients' pain intensity. Third, like healthy controls, FM patients normally detect and experience a full range of perceived pain

magnitude; but sensations become unpleasant at stimulus intensities that are significantly lower than those observed in healthy controls. Fourth, while commonly associated with chronic pain, depression does not appear to influence the sensory-discriminative dimension of pain in FM. Fifth, attitudes and beliefs such as locus of control and catastrophizing appear to be influential in the processing of sensory-discriminative aspects of pain. Sixth, FM patients utilize more extensive brain resources than do same-aged peers in order to achieve comparable performance on cognitive tasks.

Limitations and future potential of fMRI in fibromyalgia

Currently, most fMRI activation studies can only assess the effects of short interventions that can be turned 'on' and 'off' repeatedly within seconds to a minute. Thus, conventional fMRI cannot directly assess the effect of an oral analgesic on the clinical pain of FM but can assess the interaction of the analgesic with a repeated brief stimulus such as painful heat or pressure. Newer MRI methodologies are changing this limitation and expanding the types of physiological variables that can be evaluated by functional brain imaging. Magnetic resonance perfusion can assess cerebral blood flow and cerebral blood volume, providing measures of baseline differences similar to that currently provided by PET. Diffusion tensor imaging, another variant of fMRI, provides a non-invasive, *in vivo* assessment of water molecular diffusion that reflects tissue configuration at a microscopic level in white matter regions. Quantification of water diffusion will improve the neuro-radiological assessment of a variety of gray and white matter disorders, including those involved in pain processing. Yet another new approach, magnetic resonance spectroscopy, obtains spectra of multiple selected regions and determines the ratio of concentrations of metabolites such as N-acetyl-aspartate, creatine, choline, lactate, glucose and glutamate. Usually, a particular stable metabolite (for example, creatine) is used as a standard and the concentration of the test metabolites are expressed as a ratio to this standard. Abnormalities in the levels of these metabolites are associated with a number of pathological changes in brain tissue. This method has been applied to patients with chronic low back pain, showing reductions of N-acetyl-aspartate and glucose in dorsolateral prefrontal cortex compared to control subjects [56].

These recent applications of functional neuroimaging have provided evidence for a centralized pain augmentation in FM and identified brain regions that may be involved in this augmentation. Advances in design and new imaging technologies promise to further increase our understanding of the mechanisms that initiate and maintain this disorder, and can lead to improved diagnosis and treatment.

This review is part of a series on
Biology and therapy of fibromyalgia
edited by Leslie Crofford.

Other articles in this series can be found at
http://arthritis-research.com/articles/
review-series.asp?series=ar_fibromyalgia

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

Preparation of the manuscript was supported in part by Department of Army grant DAMD17-00-2-0018.

References

1. Goldenberg DL: **Office management of fibromyalgia.** *Rheum Dis Clin North Am* 2002, **28:**437-446, xi.
2. Brecher LS, Cymet TC: **A practical approach to fibromyalgia.** *J Am Osteopath Assoc* 2001, **101:**S12-S17.
3. Sprott H: **What can rehabilitation interventions achieve in patients with primary fibromyalgia?** *Curr Opin Rheumatol* 2003, **15:**145-150.
4. Penrod JR, Bernatsky S, Adam V, Baron M, Dayan N, Dobkin PL: **Health services costs and their determinants in women with fibromyalgia.** *J Rheumatol* 2004, **31:**1391-1398.
5. Forseth KO, Gran JT: **Management of fibromyalgia: what are the best treatment choices?** *Drugs* 2002, **62:**577-592.
6. Wolfe F, Anderson J, Harkness D, Bennett RM, Caro XJ, Goldenberg DL, Russell IJ, Yunus MB: **A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia.** *Arthritis Rheum* 1997, **40:**1560-1570.
7. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P: **The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee.** *Arthritis Rheum* 1990, **33:**160-172.
8. Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH: **Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation.** *Pain* 2003, **105:**403-413.
9. Price DD, Hu J, Dubner R, Gracely RH: **Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses.** *Pain* 1977, **3:5**7-68.
10. Jones AK: **The contribution of functional imaging techniques to our understanding of rheumatic pain.** *Rheum Dis Clin North Am* 1999, **25:**123-152.
11. Sawamoto N, Honda M, Okada T, Hanakawa T, Kanda M, Fukuyama H, Konishi J, Shibasaki H: **Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: an event-related functional magnetic resonance imaging study.** *J Neurosci* 2000, **20:**7438-7445.
12. Treede RD, Kenshalo DR, Gracely RH, Jones AK: **The cortical representation of pain.** *Pain* 1999, **79:**105-111.
13. Coghill RC, Sang CN, Maisog JM, Iadarola MJ: **Pain intensity processing within the human brain: A bilateral, distributed mechanism.** *J Neurophysiol* 1999, **82:**1934-1943.
14. Rainville P: **Brain mechanisms of pain affect and pain modulation.** *Curr Opin Neurobiol* 2002, **12:**195-204.
15. Koyama T, Kato K, Mikami A: **During pain-avoidance neurons activated in the macaque anterior cingulate and caudate.** *Neurosci Lett* 2000, **283:**17-20.
16. Desbois C, Villanueva L: **The organization of lateral ventromedial thalamic connections in the rat: a link for the distribution of nociceptive signals to widespread cortical regions.** *Neuroscience* 2001, **102:**885-898.
17. Bourgeais L, Gauriau C, Bernard JF: **Projections from the nociceptive area of the central nucleus of the amygdala to the forebrain: a PHA-L study in the rat.** *Eur J Neurosci* 2001, **14:** 229-255.
18. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK: **Human brain mechanisms of pain perception and regulation in health and disease.** *Eur J Pain* 2005, **9:**463-484.
19. Koyama T, McHaffie JG, Laurienti PJ, Coghill RC: **The subjective experience of pain: where expectations become reality.** *Proc Natl Acad Sci USA* 2005, **102:**12950-12955.

20. Mountz JM, Bradley LA, Modell JG, Alexander RW, Triana-Alexander M, Aaron LA, Stewart KE, Alarcon GS, Mountz JD: **Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels.** *Arthritis Rheum* 1995, **38:**926-938.
21. Kwiatek R, Barnden L, Tedman R, Jarrett R, Chew J, Rowe C, Pile K: **Regional cerebral blood flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami.** *Arthritis Rheum* 2000, **43:**2823-2833.
22. Bradley LA, Sotolongo A, Alberts KR, Alarcon GS, Mountz JM, Liu HG, Kersh BC, Domino ML, De Waal D, Weigent DA, Blalock JE: **Abnormal regional cerebral blood flow in the caudate nucleus among fibromyalgia patients and non-patients is associated with insidious symptom onset.** *J Musculoskeletal Pain* 1999, **7:** 285-292.
23. Iadarola MJ, Max MB, Berman KF, Byas-Smith MG, Coghill RC, Gracely RH, Bennett GJ: **Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain.** *Pain* 1995, **63:**55-64.
24. Di Piero V, Jones AK, Iannotti F, Powell M, Perani D, Lenzi GL, Frackowiak RS: **Chronic pain: A PET study of the central effects of percutaneous high cervical cordotomy.** *Pain* 1991, **46:**9-12.
25. Ness TJ, San Pedro EC, Richards JS, Kezar L, Liu HG, Mountz JM: **A case of spinal cord injury-related pain with baseline rCBF brain SPECT imaging and beneficial response to gabapentin.** *Pain* 1998, **78:**139-143.
26. San Pedro EC, Mountz JM, Mountz JD, Liu HG, Katholi CR, Deutsch G: **Familial painful restless legs syndrome correlates with pain dependent variation of blood flow to the caudate, thalamus, and anterior cingulate gyrus.** *J Rheumatol* 1998, **25:** 2270-2275.
27. Sorkin LS, McAdoo DJ, Willis WD: **Stimulation in the ventral posterior lateral nucleus of the primate thalamus leads to release of serotonin in the lumbar spinal cord.** *Brain Res* 1992, **581:**307-310.
28. Chudler EH, Sugiyama K, Dong WK: **Nociceptive responses in the neostriatum and globus pallidus of the anesthetized rat.** *J Neurophysiol* 1993, **69:**1890-1903.
29. Diorio D, Viau V, Meaney MJ: **The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress.** *J Neurosci* 1993, **13:** 3839-3847.
30. Lineberry CG, Vierck CJ: **Attenuation of pain reactivity by caudate nucleus stimulation in monkeys.** *Brain Res* 1975, **98:** 119-134.
31. Acupuncture Anesthesia Coordinating Group: **Observations on electrical stimulation of the caudate nucleus of human brain and acupuncture in treatment of intractable pain.** *Chin Med J (Engl)* 1977, **3:**117-124.
32. Gracely RH, Lota L, Walter DJ, Dubner R: **A multiple random staircase method of psychophysical pain assessment.** *Pain* 1988, **32:**55-63.
33. Gracely RH, Petzke F, Wolf JM, Clauw DJ: **Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia.** *Arthritis Rheum* 2002, **46:**1333-1343.
34. Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH: **Functional imaging of pain in patients with primary fibromyalgia.** *J Rheumatol* 2004, **31:**364-378.
35. Grant MA, Farrell MJ, Kumar R, Clauw DJ, Gracely RH: **fMRI evaluation of pain intensity coding in fibromyalgia patients and controls [abstract].** *Arthritis Rheum* 2001, **44:**S394.
36. Giesecke T, Gracely R H, Williams DA, Geisser M, Petzke F, Clauw DJ: **The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort.** *Arthritis Rheum* 2005, **52:**1577-1584.
37. Crisson JE, Keefe FJ: **The relationship of locus of control to pain coping strategies and psychological distress in chronic pain patients.** *Pain* 1988, **35:**147-154.
38. Rudy TE, Kerns RD, Turk DC: **Chronic pain and depression: toward a cognitive-behavioral mediation model.** *Pain* 1988, **35:**129-140.
39. Jensen MP, Turner JA, Romano JM, Karoly P: **Coping with chronic pain: A critical review of the literature.** *Pain* 1991, **47:** 249-283.
40. Strong J, Ashton R, Cramond T, Chant D: **Pain intensity, attitude and function in back pain patients.** *Aus Occupational Therapy J* 1990, **37:**179-183.
41. Gibson SJ, Helme RD: **Cognitive factors and the experience of pain and suffering in older persons.** *Pain* 2000, **85:**375-383.
42. Lipchik GL, Milles K, Covington EC: **The effects of multidisciplinary pain management treatment on locus of control and pain beliefs in chronic non-terminal pain.** *Clin J Pain* 1993, **9:**49-57.
43. Hagglund KJ, Haley WE, Reveille JD, Alarcon GS: **Predicting individual diffrences in pain and functional impairment amoung patients with rheumatoid arthritis.** *Arthritis Rheum* 1989, **32:**851-858.
44. Flor H, Turk DC: **Chronic back pain and rheumatoid arthritis: predicting pain and disability from cognitive variables.** *J Behav Med* 1988, **11:**251-265.
45. Parker JC, Frank RG, Beck NC, Smarr KL, Buescher KL, Phillips LR, Smith EI, Anderson SK, Walker SE: **Pain management in rheumatoid arthritis patients. A cognitive-behavioral approach.** *Arthritis Rheum* 1988, **31:**593-601.
46. Pastor MA, Salas E, Lopez S, Rodriguez J, Sanchez S, Pascual E: **Patients' beliefs about their lack of pain control in primary fibromyalgia syndrome.** *Br J Rheumatol* 1993, **32:**484-489.
47. McCarberg B, Wolf J, Oliver K, Fakhry F, Walen H, Cronan T: **The relationship between health locus of control and well-being in fibromyalgia patients.** *Jof Pain* 2002, **3:**14.
48. Burckhardt CS, Bjelle A: **Perceived control: A comparison of women with fibromyalgia, rheumatoid arthritis, and systemic lupus erythematosus using a Swedish version of the Rheumatology Attitudes Index.** *Scand J Rheumatol* 1996, **25:** 300-306.
49. Gustafsson M, Gaston-Johansson F: **Pain intensity and health locus of control: A comparison of patients with fibromyalgia syndrome and rheumatoid arthritis.** *Patient Educ Couns* 1996, **29:**179-188.
50. Farrell MJ, VanMeter JW, Petzke F, Wolfe JM, Grant MAB, Clauw DJ, Gracely RH: **Supraspinal activity associated with painful pressure in fibromyalgia is associated with beliefs about locus of pain control [abstract].** *Arthritis Rheum* 2001, **44:**S394.
51. Skevington SM: **A standardized scale to measure beliefs about controlling pain (BPCQ): A preliminary study.** *Psychol Health* 1990, **4:**221-232.
52. Burton AK, Tillotson KM, Main CJ, Hollis S: **Psychosocial predictors of outcome in acute and subchronic low back trouble.** *Spine* 1995, **20:**722-728.
53. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ: **Pain catastrophizing and neural responses to pain among persons with fibromyalgia.** *Brain* 2004, **127:**835-843.
54. Park DC, Glass JM, Minear M, Crofford LJ: **Cognitive function in fibromyalgia patients.** *Arthritis Rheum* 2001, **44:**2125-2133.
55. Bangert AS, Glass JM, Welsh RC, Crofford LJ, Taylor SF, Park DC: **Functional magnetic resonance imaging of working memory in fibromyalgia [abstract].** *Arthritis Rheum* 2003, **48:** S90.
56. Grachev ID, Fredrickson BE, Apkarian AV: **Brain chemistry reflects dual states of pain and anxiety in chronic low back pain.** *J Neural Transm* 2002, **109:**1309-1334.

APPENDIX E.

Referenced Abstract Presentations

Presentation: Glutamate in the Anterior Insula Is Associated with Working Memory Performance in Fibromyalgia (FM) (ACR/ARHP Annual Scientific Meeting)

Wednesday, October 21, 2009: 9:30 AM
112 A (Pennsylvania Convention Center)

*Paloma Barjola[1], **Jennifer Glass**[2], Pia Sundgren[2], Steven E. Harte[2], David A. Williams[2], Daniel Clauw[3] and Richard Harris[2], [1]Rey Juan Carlos, Madrid, Spain, [2]U. Michigan, Ann Arbor, MI, [3]University of Michigan, Ann Arbor, MI*
Presentation Number: 1993

Purpose: Glutamate (Glu) is an excitatory neurotransmitter whose concentration within the posterior insula has been shown to be related to pain processing in fibromyalgia (FM) (Harris et al. 2008). The role of Glu in the anterior insula in FM is less understood. Since FM is also associated with multiple cognitive impairments such as reduced working memory (WM), and insular structures have been previously shown to be involved in different aspects of memory function, we hypothesized that anterior insular Glu may be related to WM performance.
Method: 19 FM patients (age 45.2 (15) yrs) participated in a session of H-MRS and single-voxel spectroscopy (SVS) was performed using the following parameters: PRESS, TR 3000ms, TE 30 ms, 90° flip angle, NEX 8, FOV 16cm, and VOI of 2x2x3cm. Two separate SVS sequences were performed, one with the VOI placed in the right anterior insula and another in the right posterior insula. Patients were at rest during the session. Values for Glu were calculated as absolute concentration using water signal as an internal reference, and expressed in arbitrary institutional units (AIU). Raw data were analyzed with LCModel software. WM performance was assessed with the Letter-Number span test (Wechsler Memory Scale). Additionally, reported pain was assessed with the McGill Pain Questionnaire (MPQ). Data were analyzed with SPSS v17.

Results: Concentrations of Glu in the right anterior insula were positively correlated with WM performance (r=0.626; p=0.004). The sensory subscale, but not the affective subscale, of MPQ was negatively correlated with the scores in WM (r=-0.495; p=0.037). A stepwise linear regression model with WM performance as a dependent variable was carried out. In the first step pain showed significance as a predictor (p=0.037) of WM (worse pain was associated with worse WM). When both pain and Glu levels were entered as simultaneous predictors, the effect of Glu was significant (p=0.014) and pain displayed a trend towards significance (p=0.104). No such relationships were detected for the right posterior insula.

Conclusion: Consistent with previous literature, the anterior and posterior regions of the insula appear to be functionally distinct. This study suggests that anterior insula Glu may be involved in WM whereas previous studies suggest that the posterior insula is involved in pain processing. Future studies are needed to understand the mechanisms underlying these relationships which may be relevant to other chronic pain populations.

Association between experimental and clinical pain measures in persons with fibromyalgia and chronic fatigue syndrome

Year: 2005

Poster #: 672

Title: Association between experimental and clinical pain measures in persons with fibromyalgia and chronic fatigue syndrome

Authors: M. Geisser, D. Clauw, D. Williams, R. Patel, R. Gracely; University of Michigan, Ann Arbor, MI

Classification: Disease Entities (Human)

Themes: C07 - Myofascial Pain & Fibromyalgia

Description:

Evoked pain is often used as a model for the study of clinical pain, yet there is little data regarding the relationship between the two. In addition, there is little data regarding the types of stimuli and stimulus intensities that are most closely related to clinical pain. In this study, 38 subjects who fulfilled the criteria for a diagnosis of fibromyalgia (FM), chronic fatigue syndrome (CFS), or both syndromes were administered measures of clinical pain. In addition, subjects underwent experimental testing utilizing heat and pressure stimulation. Stimulation levels evoking low, moderate and high intensity and comparable levels of unpleasantness were determined for both types of stimuli using random staircase methods. Clinical pain was assessed using visual analogue ratings of “pain during the past month” and “pain today”, in addition to the present pain intensity and total pain rating index from the short form of the McGill Pain Questionnaire (MPQ). Heat was not significantly associated with clinical pain ratings, with the exception of unpleasantness ratings at high stimulus intensities. Both intensity and unpleasantness ratings of pressure were significantly associated with clinical pain at low, moderate and high levels, and the strength of the association increased at higher stimulus intensities. For example, the association between MPQ scores and pressure stimulation was -.44 ($p < .01$) at ratings of low intensity, -.49 ($p < .01$) at ratings of moderate intensity, and -.52 ($p < .01$) at high intensities. These findings suggest that pressure stimulation as an experimental pain model in these populations more closely reflect the clinical pain for these conditions. This likely reflects the fact that FM as a clinical syndrome is characterized primarily by tenderness. These findings merit consideration when designing experimental studies of FM and CFS.

Baseline heart rate variability predicts increased pain after sleep restriction in healthy adults

Year: 2008

Poster #: 159

Title: Baseline heart rate variability predicts increased pain after sleep restriction in healthy adults

Authors: J Glass, A Lyden, K Ambrose, K Groner, R Gracely, D Williams, D Clauw; University of Michigan, Ann Arbor, MI

Classification: Disease Entities (Human)

Themes: C07 - Myofascial Pain & Fibromyalgia

Description:
Chronic pain disorders such as fibromyalgia (FM) are often precipitated by a “stressful” event (e.g., motor vehicle accident) that prevents normal sleep and exercise. We hypothesize that “stressors” disrupt regular sleep and exercise routines, and that this leads to increased pain and other symptoms. Furthermore, we hypothesize that individuals are not equally susceptible, and neurobiological factors can predict if an otherwise healthy individual will respond to disrupted sleep or exercise with an acute increase in pain. Eighty-three participants who were regular runners and who slept 7-9 hours per night took part. Participants were randomly assigned to one of four groups: control, exercise deprivation, sleep restriction (6 hours per night), or both exercise and sleep restriction. The deprivation period lasted 10 days. Pain and other symptoms (fatigue, mood & dyscognition) were assessed at baseline and the end of the study. Measures of pain included self-report and pressure sensitivity. Autonomic nervous system function was assessed via heart rate variability (HRV) at baseline. Correlations were calculated (for the participants assigned to a deprivation condition) between baseline HRV measures and changes in pain. Sleep restriction but not exercise deprivation resulted in significant increases in self-reported and evoked pain. Baseline HRV parameters were strongly correlated with increased pain. Total power, very low and ultra low frequencies were related to self-report pain (e.g., $r=-.568$, $p < .001$) and high frequency HRV was related to pressure pain threshold ($r=.369$, $p <.04$). Amongst a group of healthy, symptom-free individuals, baseline neuro-physiological measures (HRV) predicted subsequent increases in pain. These data suggest that the autonomic nervous system dysfunction observed in FM represents a diathesis that predisposes individuals to development of pain after exposure to a stressor. Furthermore, the results highlight the individual variability in response to stressors, and extend prior work using different sleep deprivation procedures.

Presentation: Effects of Sleep Restriction and Exercise Deprivation on Mood, Pain, Fatigue, Somatic Symptoms and Cognition in Healthy Adults (2007)

Introduction. It is known that good sleep hygiene and regular exercise can improve FM symptoms. We hypothesized that disrupted sleep and exercise routines may be part of the etiology of chronic FM symptoms. Individually, sleep or exercise deprivation can result in increased symptoms of pain, negative mood, fatigue, and dyscognition. In this study, we examined the independent and combined effects of exercise deprivation and sleep restriction in healthy, regularly exercising adults.

Methods. Eighty-three participants who regularly ran at least 5 times per week and who slept 7-9 hours per night took part in the study. Participants were randomly assigned to one of four groups: control (normal activity and sleep), exercise deprivation, sleep restriction (6 contiguous hours in bed per night), or both exercise and sleep restriction. The deprivation period lasted 10 days. Symptoms were assessed at baseline and near the end of the deprivation period. Symptom domains included pain (self-report and evoked pressure pain sensitivity), fatigue, mood, and dyscognition (self-report and performance measures). Each symptom domain was analyzed with a 2 (pre- and post-deprivation) by 2 (sleep) by 2 (exercise) ANOVA to assess main effects and interaction between sleep restriction and exercise deprivation.

Results. There was a significant main effect of sleep for all symptom domains. For example, McGill VAS pain increased ($F(1, 80) = 8.794$, $p = .004$), fatigue increased ($F(1,80)=37.00$, $p < .001$), negative mood increased ($F(1,80)=13.41$, $p < .001$), and dyscognition increased ($F(1,80) = 10.98$, $p = .001$). Exercise deprivation had more limited effects on pressure pain sensitivity ($F(1, 80) = 9.93$, $p =.003$), fatigue ($F(1, 80) = 5.97$, $p = .019$) and negative mood ($F(1, 80) = 5.28$, $p = .028$. Surprisingly, there were no significant interactions between sleep and exercise.

Conclusions. Among healthy regularly exercising and sleeping individuals, disruption of a normal routine was associated with increased pain, fatigue, negative mood, and dyscognition. Sleep restriction produced more widespread and severe symptoms than exercise deprivation.

Presentation: Effects of Sleep Restriction and Exercise Deprivation on Mood, Pain, Fatigue, Somatic Symptoms and Cognition in Healthy Adults (2007)

Introduction. It is known that good sleep hygiene and regular exercise can improve FM symptoms. We hypothesized that disrupted sleep and exercise routines may be part of the etiology of chronic FM symptoms. Individually, sleep or exercise deprivation can result in increased symptoms of pain, negative mood, fatigue, and dyscognition. In this study, we examined the independent and combined effects of exercise deprivation and sleep restriction in healthy, regularly exercising adults.

Methods. Eighty-three participants who regularly ran at least 5 times per week and who slept 7-9 hours per night took part in the study. Participants were randomly assigned to one of four groups: control (normal activity and sleep), exercise deprivation, sleep restriction (6 contiguous hours in bed per night), or both exercise and sleep restriction. The deprivation period lasted 10 days. Symptoms were assessed at baseline and near the end of the deprivation period. Symptom domains included pain (self-report and evoked pressure pain sensitivity), fatigue, mood, and dyscognition (self-report and performance measures). Each symptom domain was analyzed with a 2 (pre- and post-deprivation) by 2 (sleep) by 2 (exercise) ANOVA to assess main effects and interaction between sleep restriction and exercise deprivation.

Results. There was a significant main effect of sleep for all symptom domains. For example, McGill VAS pain increased ($F(1, 80) = 8.794$, $p = .004$), fatigue increased ($F(1,80)=37.00$, $p < .001$), negative mood increased ($F(1,80)=13.41$, $p < .001$), and dyscognition increased ($F(1,80) = 10.98$, $p = .001$). Exercise deprivation had more limited effects on pressure pain sensitivity ($F(1, 80) = 9.93$, $p =.003$), fatigue ($F(1, 80) = 5.97$, $p = .019$) and negative mood ($F(1, 80) = 5.28$, $p = .028$. Surprisingly, there were no significant interactions between sleep and exercise.

Conclusions. Among healthy regularly exercising and sleeping individuals, disruption of a normal routine was associated with increased pain, fatigue, negative mood, and dyscognition. Sleep restriction produced more widespread and severe symptoms than exercise deprivation.

Presentation: Increased Symptoms of Pain, Fatigue, Cognitive Problems and Negative Mood after Exercise Deprivation and Sleep Restriction are Predicted By Baseline Autonomic and HPA Function (2006)

Introduction. Chronic pain disorders such as fibromyalgia are often precipitated by an event that prevents normal sleep and exercise. We hypothesize that sleep restriction and exercise deprivation can act as stressors, and that neurobiological factors can predict if an otherwise healthy individuals will respond to such stress with an acute increase in symptoms of pain, fatigue, cognitive problems and negative mood.

Method. In an ongoing study, the initial 36 participants are the subject of this report. These healthy adults (ages 18-41 years) ran at least five times per week and slept 7-9 hours per night. Subjects were randomly assigned to one of four groups: control (normal activity and sleep), exercise deprivation, sleep restriction (6 contiguous hours in bed per night), or both exercise and sleep restriction. The deprivation period lasted 10 days. At baseline and near the end of the deprivation period somatic symptoms, heart rate variability (HRV; ultra-low frequency, very-low frequency, and total power) and salivary cortisol (taken in the morning after awakening) were obtained. Pearson product moment correlations were calculated to assess the association between baseline HRV and am cortisol measures and changes in symptoms (deprivation minus baseline).

Results. Strong negative correlations were observed between the HRV measures and changes in self-reported pain (McGill sensory, present pain index and VAS; r values between -.260 and -.706); between HRV measures and changes in cognitive performance (PVT and word-list recall; r values between -.270 and -.534). Strong negative correlations were observed between am cortisol and changes in mood (CESD, anxiety, Profile of Mood States; r values between -.306 and -.599); between am cortisol and change in fatigue (Multidimensional Fatigue Index-general, r = -.457); and between am cortisol and changes in cognitive performance (PVT, r = -.466 and word-list recall, r = -.542).

Conclusions. These results confirm that baseline physiological measures can predict subsequent increases in symptoms after sleep and exercise restriction, and are consistent with the hypothesis that low HPA and ANS function represent a diathesis that predisposes individuals to development of somatic and cognitive symptoms after exposure to a stressor.

Presentation: Sex Differences in Predictors of Increased Symptoms after Exercise and Sleep Restriction (ACR/ARHP Annual Scientific Meeting)

Tuesday, October 20, 2009: 9:00 AM - 11:00 AM
Hall D (Pennsylvania Convention Center)

Jennifer M. Glass[1], *Jacob N. Ablin*[2], *Angela Lyden*[1], *Kirsten Ambrose*[3], *David A. Williams*[1], *Richard Gracely*[4] *and Daniel Clauw*[5], [1]*U. Michigan, Ann Arbor, MI,* [2]*Rheumatology Institute, Tel Aviv, Tel Aviv, Israel,* [3]*Algynomics, Inc, Chapel Hill, NC,* [4]*U. North Carolina, Chapel Hill, NC,* [5]*University of Michigan, Ann Arbor, MI*
Presentation Number: 1428
Poster Board Number: 161

Purpose: Chronic pain disorders such as fibromyalgia are often precipitated by an event that prevents normal sleep and exercise. We hypothesize that sleep restriction and exercise deprivation can act as stressors, and that neurobiological factors can predict if an otherwise healthy individuals will respond to such stress with an acute increase in symptoms of pain, fatigue, cognitive problems and negative mood. Previously, we reported preliminary results where heart rate variability (HRV) measures were significantly correlated with symptoms after sleep and exercise restriction. Here, we report our findings on sex differences in the relationship between HRV and increased symptoms.

Method: Eighty-seven (45 male) healthy adults ages 18-41 years were included who ran at least five times per week and slept 7-9 hours per night. Subjects were randomly assigned to one of four groups: control (normal activity and sleep), exercise deprivation, sleep restriction (6 contiguous hours in bed per night), or both exercise and sleep restriction. The deprivation period lasted 10 days. At baseline, HRV was measured via 24 hour holter readings. We assessed symptom development in 5 domains: pain (McGill VAS), mood (CES-D, POMS, STPI-anxiety), fatigue (Multiple Fatigue Index), somatic symptoms (Modified Somatic Perceptions Questionnaire) and cognition (Multiple Ability Self-Report Questionnaire) at baseline and between days 7-8 of the deprivation period. For initial analyses, a Total Symptom change variable was calculated. Pearson product moment correlations were calculated to assess the association between baseline HRV and changes in symptoms.

Results: Sleep restriction led to increased symptoms across domains (reported separately). However, not all subjects reported increased symptoms. Total Symptom change ranged from -12 to +11. Women were more likely (65%) to report increased symptoms than men (40%). Among men, strong negative correlations were observed between Total Symptom Change and 24-hr total power (TP; r = -.579) as well as 24-hr ultra low frequency (ULF; r = -.628). Among women, there were no significant correlations between Total Symptom Change and any HRV measure (r values < -.180). Among men, all 5 individual symptom domains were significantly correlated with both TP and ULF (r values between -.388 and -.599).

Conclusion: We have shown that sleep restriction leads to increased symptoms of pain, fatigue, mood, cognition, and somatic complaints, especially among women. Somewhat paradoxically, neurobiological measures of autonomic nervous system function were only correlated with increased symptoms in men. However, our results are consistent with previous research on heart rate reactivity and variability to painful stimuli that suggest dramatically different sympathetic regulation of pain in men and women.

Keywords: exercise, fibromyalgia and pain

Presentation: DNIC Activation of vPAG is Absent in Fibromyalgia (2006)

Introduction: Application of a pain stimulus in animals and humans produces a widespread analgesia termed “diffuse noxious inhibitory controls” (DNIC). DNIC has been noted to be deficient in several studies of patients of fibromyalgia (FM). This association with a lack of intrinsic analgesia and augmented pain sensitivity suggest that a defect in intrinsic analgesia may mediate the pain and hyperalgesia in FM. Intrinsic analgesic systems such as DNIC have been localized in the brainstem. This study used fMRI to assess the effects of DNIC on brainstem activity in FM and healthy controls (HC).

Methods: Eleven female patients (mean age = 45) satisfying ACR criteria for FM and 10 matched HC (mean age = 45) participated in two sessions. Before fMRI scanning, the effects of painful pressure applied to the left thumbnail were assessed using the Multiple Random Staircase method and a verbal-numerical Box pain scale which determined stimulus pressures sufficient to evoke subjective levels of mild, moderate or intense pain sensations. During 6 min fMRI scans, these pressures were applied to the thumbnail in random sequence during alternating 25s blocks of painful pressure and pressure release. In one 6-min scan, a DNIC pressure stimulus was delivered to the right thumbnail at a level sufficient to evoke moderately intense pain. fMRI data were acquired by a 3.0 Tesla GE Sigma scanner (LX [VH3] release), Neuro-optimized gradients (FOV = 22, T2*-weighted, single-shot, reverse spiral acquisition, GRE, TR = 2500, TE = 30, FA = 90, 64 x 64). Analysis of the BOLD signal (head motion correction, slice timing corrections, spatial smoothed 6mm FWHM, intensity normalization, conversion to standard coordinate system, statistical comparison of pressure and pressure release conditions) was performed using Medx.

Results: Comparing DNIC to pre-DNIC baseline in HC, the most significant effect of pain evoked activity was observed in ventral periaqueductal gray (vPAG, Talairach coordinates: 6 14 -4, Z=4.27). Similar brain stem activations (DNIC -pre DNIC baseline) were not observed in FM. A statistical comparison of the DNIC effect between groups using a random effects model showed significantly greater activity in vPAG (4, -16 -6, Z=3.49) in HC, and less activity in regions implicated in pain processing (contralateral primary somatosensory cortex, Z=3.31; cerebellum, Z=3.09; Inferior parietal lobule (BA 40), Z=2.69; Thalamus (Medial Dorsal Nucleus), Z=2.63; secondary somatosensory cortex, Z=2.57).

Conclusion: A large body of evidence indicates that the vPAG is involved in intrinsic descending analgesia. The demonstration of vPAG activation only in HC and decreased activity in pain processing regions in HC is consistent with previous demonstrations of defective DNIC in FM and suggests that this defect is associated with dysfunction of the intrinsic descending vPAG-mediated system.

Presentation: Accentuated Pain Processing Despite Decreased mu-Opioid Receptor (MOR) Availability in Fibromyalgia (2006)

R.E. Harris, **D.J. Scott**, **G.A. Naylor**, **J.B. Romond**, **A.R. Bradford**, **D. Dadabhoy**, **R.H. Gracely**, **J. Zubieta**,; **D.J. Clauw**,

Purpose: Amplification of central neural pain pathways and dysfunction of endogenous antinociceptive mechanisms have both been implicated in fibromyalgia (FM). Here we investigate these two processes using two divergent brain imaging methods within the same participants.

Methods: PET - 11 female FM patients (ages 27-68) and 11 age- and sex-matched pain free controls (ages 21-55) underwent a positron emission tomography scan with [^{11}C]carfentanil, a MOR selective radiotracer. Logan plots were created to obtain maps of whole-brain MOR binding potential (BP) at baseline. [^{11}C]carfentanil binding was assessed using SPM99, and regions showing significant differences in BP between patients and controls were extracted using locally developed software. Correlations between pain report and MOR occupancy were performed in SPSS. fMRI - The same 11 FM patients were age- and sex-matched to a separate group of 19 pain free controls (ages 23-58). Participants underwent a functional magnetic resonance imaging session wherein multiple pressures were applied to the thumbnail bed in pseudo-random order. Pre-processing of images was done with SPM2 and resulting contrast images (2kg/cm^2 pressure vs. no touch) were analyzed at the group level. fMRI activations were correlated with MOR binding using SPSS. Clinical pain intensity and unpleasantness were also assessed.

Results: In the fMRI studies, during pressure pain of equal stimulus intensity, the FM patients exhibited greater neuronal activations in the bilateral insula (right: $p<0.005$; left: $p<0.01$). In the PET studies, FM patients displayed reduced MOR BP in the nucleus accumbens (bilateral: left, $p < 0.0001$; right, $p < .01$) and left amygdala ($p < .02$). Binding within the accumbens was negatively correlated with clinical pain report (GBS: rho=-0.65 to -0.79; all $p<0.05$). Interestingly MOR binding in the left amygdala (rho=-0.68; $p<0.05$), but not the nucleus accumbens ($p>0.5$), was negatively correlated with evoked pain fMRI activations within the insula.

Conclusion: Even though FM patients exhibited augmented central pain processing in the fMRI study, these same patients showed decreased MOR BP in multiple brain regions. This suggests that the augmented pain processing in FM is not due to a attenuated function of the intrinsic opioid system, and also shows the potential value of using multiple functional imaging techniques simultaneously. Furthermore these data may help explain why FM patients seem to be less responsive to exogenously administered opioids as MOR availability is reduced potentially leading to decreased availability for binding to exogenous ligands.

Presentation: Longitudinal Changes in Pressure Pain Sensitivity Vary with Insular Neuronal Activity in Fibromyalgia Patients (2006)

R.E. Harris, D.J. Scott, G.A. Naylor, J.B. Romond, A.R. Bradford, R.H. Gracely, J. Zubieta, D.J. Clauw,

Purpose: Previous cross-sectional studies using functional MRI (fMRI) have noted augmented central pain processing in fibromyalgia (FM). However less attention has been paid to fluctuating pain and tenderness levels over time, and how these changes may relate to underlying neural activity. Here we examine longitudinal changes in evoked pressure pain sensitivity in FM, and determined whether changes in this clinical parameter are accompanied by changes in fMRI-measured neural activity.

Methods: 12 female FM patients (ages 27 to 68) were randomized to receive 9 treatments of either acupuncture or sham acupuncture over the course of 4 weeks. For the purpose of this analysis both treatment groups were combined. All participants underwent two fMRI sessions, one before and one after all treatments. During fMRI, multiple pressures were applied to the thumbnail bed in pseudo-random order. Images were pre-processed with SPM2 and resulting contrast images ($2kg/cm^2$ pressure vs. no touch) were analyzed between subjects at both time points. Psychophysical pain testing using pressure stimuli of varying intensities was performed outside of the scanner. fMRI BOLD activations were correlated with psychophysical pressure ratings using SPSS.

Results: Pressure pain sensitivity was significantly reduced following 9 treatments (kg increase mean(sd): 0.30(0.27); $p<0.005$). fMRI BOLD activations in response to pressure pain were reduced after treatment in the contralateral insula ($p<0.005$). Interestingly changes in BOLD activations within both the posterior and anterior insula were negatively correlated with changes in pressure pain sensitivity assessed outside of the scanner (anterior: rho=-0.84; $p<0.005$; posterior: rho=-0.64; $p<0.05$).

Conclusion: These data suggest that long-term changes in evoked pressure pain sensitivity can be achieved in FM. Furthermore, activity within the insula appears to be related to changes in pressure sensitivity. These results have implications for trials in FM, as fMRI activations within the insula could serve as a useful biomarker of pain processing.

Presentation: Differential Sustained Changes in μ-Opioid Receptor (MOR) Availability Following Acupuncture and Sham Acupuncture Therapy in Fibromyalgia (FM) (2007)

Purpose: Clinical trials of acupuncture versus sham therapy in fibromyalgia (FM) have had equivocal findings, suggesting that acupuncture may work via placebo mechanisms. Since μ-opioid receptors (MORs) are thought to be involved in both acupuncture analgesia and placebo effects, we explored long-term changes in central MOR availability using positron emission tomography (PET) in FM. We hypothesized that if traditional acupuncture and sham acupuncture work via the same mechanism, similar changes in MOR availability should be observed between groups.

Methods: 17 female FM patients (45+/-14yrs) were randomized to receive either nine traditional acupuncture (TA; n=9) or nine sham acupuncture (SA; n=8) treatments over the course of 4 weeks. TA involved insertion of 9 acupuncture needles into the body whereas SA did not involve skin penetration. The first and the ninth treatment occurred during PET imaging with ^{11}C-carfentanil, a selective MOR agonist. Each PET session lasted 90 minutes and included a 0-40 minute baseline scan prior to needle insertion. For the purposes of this analysis we compared changes in baseline scans from the first to the second PET session between groups. PET images were processed with Logan plot analysis resulting in maps of whole-brain MOR binding potential (BP; a measure of receptor availability). Images were analyzed with SPM99. Clinical pain was assessed before the first treatment and after the last with the Short Form McGill Pain Questionnaire (SF-MPQ). Correlations between changes in clinical pain and changes in the MOR BP were performed.

Results: Clinically significant improvements in pain were obtained following treatment (SF MPQ total: MeanDiff(SD) TA=5.4(9.6); SA=2.3(6.4)) although there was no between-group difference (p=.44). However significant changes in MOR BP were detected between TA and SA within 17 different brain regions (all $p<0.001$; uncorrected). These regions included: insula, amygdala, thalamus, cingulate (anterior and perigenual), caudate, prefrontal cortex, and hypothalamus. Within the anterior cingulate (ACC) improvements in clinical pain were positively correlated with increases MOR BP for TA (ACC: r=.68; p=.04) but negatively for SA (r=-.81; p=.02). Within the caudate improvements in clinical pain were positively correlated with increases in MOR BP for TA (r=.75; p=.02) but not SA (r=-.02; p=.96). Conversely, within the perigenual cingulate (pgCC) and dmPFC, improvements in clinical pain were associated with decreases in MOR BP for SA (pgCC: r=-.70; p=.05; dmPFC: r=-.73; p=0.04) but not for TA (pgCC: r=.35; p=.35; dmPFC: r=.33; p=.39).

Conclusions: The underlying mechanisms of TA and SA are not equivalent, despite similar results in clinical pain report. Further studies using larger samples will be necessary to corroborate these findings.

Presentation: Bilateral Anterior Insular Glutamate (Glu) Is Asymmetrically Associated with Experimental Pain in Individuals with Fibromyalgia and Pain-Free Controls (ACR/ARHP Annual Scientific Meeting)

Wednesday, October 21, 2009: 9:45 AM
112 A (Pennsylvania Convention Center)

Richard Harris[1], *Pia Sundgren*[1], *James Hubbard*[1], *A.D. (Bud) Craig*[2] *and Daniel Clauw*[3], [1]*U. Michigan, Ann Arbor, MI,* [2]*Atkinson Research Laboratory, Barrow Neurological Institute, Phoenix, AZ,* [3]*University of Michigan, Ann Arbor, MI*

Presentation Number: 1994

Purpose: The insula is involved in processing both sensory and affective aspects of pain. It has been suggested that there is an asymmetric distribution in function within this structure, with the right anterior insula being responsive to pain stimuli and the left playing more of a pain inhibiting role. Using proton magnetic resonance spectroscopy (H-MRS), we examined the relative levels of glutamate (Glu), an excitatory neurotransmitter, within the right and left anterior insula of individuals with fibromyalgia (FM) and pain-free controls (HC). We hypothesized that greater levels of Glu in the right anterior insula as compared to the left, would be associated with more pain sensitivity.

Methods: Subjects from an ongoing acupuncture trial in FM, with complete bilateral insula H-MRS data were studied. 11 patients (ages 47+/-18 yrs) and 14 controls (ages 46+/-11 yrs) underwent single voxel spectroscopy (SVS) using the following parameters: PRESS, TR 3000ms/TE 30ms, 90 degree flip angle, NEX 8, FOV 16, with a volume of interest (VOI) of 2x2x3cm voxel. Four separate SVS sequences were performed in the insula: 1. right anterior, 2. right posterior, 3. left anterior and 4. left posterior. Participants were at rest during the scanning session. Spectra were analyzed offline with LCModel. Values for Glu were expressed in arbitrary institutional units (AIU) using water as an internal standard. The ratio of right anterior insula Glu divided by left anterior insula Glu was calculated and entered into SPSS v.17. Analogous calculations were performed with the right and left posterior insula. Experimental pressure pain testing was performed prior to H-MRS. Data were analyzed with SPSS v.17.

Results: The ratio of right anterior insula Glu versus left anterior insula Glu was significantly correlated with pressure pain sensitivity when both groups were combined (medium pain: $r=-0.56$, $p=0.004$; high pain: $r=-0.50$, $p<0.01$), and when groups were analyzed separately (HC medium pain: $r=-0.57$, $p=0.04$; FM medium pain: $r=-0.54$; $p=0.09$). Individuals with greater Glu in the right anterior insula, as compared to the left, displayed lower pressure thresholds. This result was not obtained for the bilateral posterior insula Glu ratio (medium pain: $r=-0.36$, $p>0.05$; high pain: $r=-0.28$, $p>0.1$).

Conclusions: There appears to be an asymmetric distribution of Glu function in the anterior insulae. Greater excitatory neural activity in the right anterior insula, as compared to the left, is associated with more pain sensitivity. This relationship may represent a general aspect of pain processing.

Presentation: Bilateral Anterior Insular Glutamate (Glu) Is Asymmetrically Associated with Experimental Pain in Individuals with Fibromyalgia and Pain-Free Controls (ACR/ARHP Annual Scientific Meeting)

Wednesday, October 21, 2009: 9:45 AM
112 A (Pennsylvania Convention Center)

Richard Harris[1], *Pia Sundgren*[1], *James Hubbard*[1], *A.D. (Bud) Craig*[2] *and Daniel Clauw*[3], [1]*U. Michigan, Ann Arbor, MI,* [2]*Atkinson Research Laboratory, Barrow Neurological Institute, Phoenix, AZ,* [3]*University of Michigan, Ann Arbor, MI*
Presentation Number: 1994

Purpose: The insula is involved in processing both sensory and affective aspects of pain. It has been suggested that there is an asymmetric distribution in function within this structure, with the right anterior insula being responsive to pain stimuli and the left playing more of a pain inhibiting role. Using proton magnetic resonance spectroscopy (H-MRS), we examined the relative levels of glutamate (Glu), an excitatory neurotransmitter, within the right and left anterior insula of individuals with fibromyalgia (FM) and pain-free controls (HC). We hypothesized that greater levels of Glu in the right anterior insula as compared to the left, would be associated with more pain sensitivity.

Methods: Subjects from an ongoing acupuncture trial in FM, with complete bilateral insula H-MRS data were studied. 11 patients (ages 47+/-18 yrs) and 14 controls (ages 46+/-11 yrs) underwent single voxel spectroscopy (SVS) using the following parameters: PRESS, TR 3000ms/TE 30ms, 90 degree flip angle, NEX 8, FOV 16, with a volume of interest (VOI) of 2x2x3cm voxel. Four separate SVS sequences were performed in the insula: 1. right anterior, 2. right posterior, 3. left anterior and 4. left posterior. Participants were at rest during the scanning session. Spectra were analyzed offline with LCModel. Values for Glu were expressed in arbitrary institutional units (AIU) using water as an internal standard. The ratio of right anterior insula Glu divided by left anterior insula Glu was calculated and entered into SPSS v.17. Analogous calculations were performed with the right and left posterior insula. Experimental pressure pain testing was performed prior to H-MRS. Data were analyzed with SPSS v.17.

Results: The ratio of right anterior insula Glu versus left anterior insula Glu was significantly correlated with pressure pain sensitivity when both groups were combined (medium pain: $r=-0.56$, $p=0.004$; high pain: $r=-0.50$, $p<0.01$), and when groups were analyzed separately (HC medium pain: $r=-0.57$, $p=0.04$; FM medium pain: $r=-0.54$; $p=0.09$). Individuals with greater Glu in the right anterior insula, as compared to the left, displayed lower pressure thresholds. This result was not obtained for the bilateral posterior insula Glu ratio (medium pain: $r=-0.36$, $p>0.05$; high pain: $r=-0.28$, $p>0.1$).

Conclusions: There appears to be an asymmetric distribution of Glu function in the anterior insulae. Greater excitatory neural activity in the right anterior insula, as compared to the left, is associated with more pain sensitivity. This relationship may represent a general aspect of pain processing.

Presentation: Variation in Glutamate and Glutamine Levels within the Insula are Associated with Improvements in Clinical and Experimental Pain in Fibromyalgia (FM) (2007)

Purpose: The insula is involved in processing both sensory and affective aspects of pain. Previous functional neuroimaging studies suggest augmented neural activity within this structure in FM patients. Since glutamate (Glu) is a major excitatory neurotransmitter within the central nervous system, we used proton magnetic resonance spectroscopy (H-MRS) to investigate variations in Glu and glutamine (Gln) levels over time in FM patients. We hypothesized that reductions in Glu and/or Gln should parallel improvements in clinical pain and evoked pain sensitivity.

Methods: As part of an ongoing trial of acupuncture in FM, 10 patients (48+/- 15 yrs) underwent H-MRS prior to and following nine treatments. Single voxel spectroscopy (SVS) was performed using the following parameters: PRESS, TR 3000ms/TE 30ms, 90 degree flip angle, NEX 8, FOV 16, with a volume of interest (VOI) of 2x2x3cm voxel. Two separate SVS sequences were performed with the VOI placed first in the anterior and then the posterior insula. Patients were at rest during each session. Spectra were analyzed offline with LCModel. Values for Glu, Gln, and combined Glu+Gln (Glx) were calculated as ratios to the internal standard creatine (Cre; eg. Glu/Cre). Clinical and experimental pain were assessed pre- and post-treatment, with the Short Form of the McGill Pain questionnaire (SF-MPQ) and psychophysical pressure pain testing (multiple random staircase) respectively. Data were analyzed with SPSS v.14.

Results: Clinical pain improved over the course of treatment for the sensory but not the affective dimension of pain (SF-MPQ Mean Diff(SD): Sensory=3.5(4.7); $p=0.04$; Affective=0.1(2.5); $p>0.05$). Hyperalgesia was also significantly reduced at moderate pressures (Mean Diff(SD)=-0.34(0.46)kg; $p=0.04$). Glu/Cre, Gln/Cre, and Glx/Cre levels did not significantly change over time (all $p>0.05$), but differences in Glx/Cre and Glu/Cre (pre-post treatment) within the posterior insula were negatively correlated with changes in hyperalgesia (Glx/Cre: $r=-0.68$; $p=0.03$; Glu/Cre: $r=-0.93$; $p<0.001$). Changes in Glx/Cre levels within the anterior insula were also negatively correlated with changes in hyperalgesia ($r=-0.77$; $p=0.04$). Inter-individual variations in Glu/Cre within the posterior insula were also positively correlated with changes in clinical pain (McGill total: $r=0.80$; $p=0.005$; Sensory: $r=0.77$; $p=0.009$; Affective: $r=0.78$; $p=0.008$).

Conclusion: Insular Glu and/or Gln levels appear to change with improvements in multiple pain dimensions within FM patients. This could result from changes in glutamatergic neurotransmission within this structure. H-MRS may be a useful outcome measure in clinical trials within this population.

Presentation: Comparison Between Pressure and Thermal Conditioning Stimuli in the Evaluation of Descending Noxious Inhibitory Control (DNIC) in Fibromyalgia Patients and Healthy Controls (ACR/ARHP Annual Scientific Meeting)

Sunday, October 18, 2009: 9:00 AM - 11:00 AM
Hall D (Pennsylvania Convention Center)
*Rachel K. Harrison[1], Craig Urwin[1], Rupal Bhavsar[1], Richard E. Harris[1], **Daniel Clauw**[2] and Steven E. Harte[1], [1]U. Michigan, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI*
Presentation Number: 87
Poster Board Number: 87

Purpose: Endogenous pain modulation is commonly evaluated using DNIC testing paradigms. These procedures incorporate a conditioning stimulus (a noxious stimulus that evokes DNIC activation) and a test stimulus (a noxious stimulus used to evaluate the analgesic response to the conditioning stimulus). DNIC paradigms vary greatly in regards to experimental parameters, including the type of noxious stimuli employed. It is not clear, however, if certain parameters affect DNIC outcomes differently. Previous studies indicate that individuals with fibromyalgia (FM) have attenuated DNIC compared to pain-free controls. Therefore, we compared the effects of 2 different conditioning stimuli on DNIC activation in FM patients and healthy controls (HCs) to determine if different stimuli produce different DNIC effects.

Method: Right-handed females (FM = 18, HC = 15) underwent DNIC testing with pressure as the test stimulus, and either noxious pressure or cold water as the conditioning stimulus. Baseline intensity of the test stimulus was rated during 30-s of continuous pressure applied to the left thumbnail on a 0-100 rating scale. DNIC was induced 5-min later by applying 60-s of continuous pressure to the right thumbnail. Alternatively, subjects immersed their right hand into a 12 degree Celsius water bath for 60-s. Parallel to the last 30-s of pressure or cold water conditioning, the same test stimulus was reapplied to the left thumbnail and rated. DNIC was evaluated as the difference in pain rating of the test stimulus applied before and during the conditioning stimulus.

Results: Differences in DNIC between groups were assessed with separate repeated measures general linear models, one for pressure and one for cold water. Preliminary data indicate a significant GROUP X DNIC interaction when pressure was used as the conditioning stimulus, $p = 0.038$. Ratings of the test stimulus taken before and during application of the pressure conditioning stimulus revealed DNIC-induced analgesia in HCs (Mean ± SD, 57.83 ± 18.07 vs. 40.17 ± 24.90). In contrast, FM patients exhibited hyperalgesia during concomitant pressure stimulation (57.70 ± 26.32 vs. 64.00 ± 24.90). When cold water was used as the conditioning stimulus, modest differences in DNIC were observed between HCs (58.17 ± 22.19 vs. 39.03 ± 21.81) and FM patients (60.10 ± 20.95 vs. 51.00 ± 27.09), however no significant GROUP X DNIC interaction was found, $p > 0.30$.

Conclusion: These data suggest that DNIC testing using pressure as both a conditioning and test stimulus identifies attenuated DNIC in FM. The cold water conditioning stimulus led to less robust differences between FM patients and HCs. In contrast to other DNIC paradigms that either use sophisticated and/or expensive test stimuli (e.g. thermal probes), or very noxious conditioning stimuli that individuals may be reluctant to undergo repeatedly, this paradigm can be performed longitudinally in nearly any setting.

Keywords: outcome measures and pain

Disclosure: R. K. Harrison, None; **C. Urwin**, None; **R. Bhavsar**, None; **R. E. Harris**, None; **D. Clauw**, UCB, 5, Forest Laboratories, 5, Pfizer Inc, 5, Lilly , 5, Cypress Biosciences Inc, 5, Forest Laboratories , 2, Pfizer Inc, 2, Astra-Zeneca, 5, Pierre-Fabre, 5 ; **S. E. Harte**, None.
<< Previous Abstract in Session | Next Abstract in Session >>
See more of: Fibromyalgia and Soft Tissue Disorders
See more of: ACR Poster Sessions

Presentation: Catastrophizing and Fatigue are Associated with Poorer Perceived Physical Function Relative to Objective Activity Measures in Fibromyalgia (2007)

Purpose: Patients with fibromyalgia (FM) have low levels of self-reported physical function, compared to either controls or other chronic illnesses. We have previously shown that in both FM patients and controls, there are poor relationships between self-reported function, and objective activity levels as measured by actigraphy. This study examined the potential reasons for the differences between self-reported function and activity levels in FM by examining the symptoms and psychological factors most strongly associated with these discrepanices.

Methods: 31 patients with FM (43.1 ± 8.2 years, 71% women) completed 5 days of ambulatory monitoring of physical activity, using a wristwatch-sized omni-directional accelerometer (Actiwatch-Score). Activity counts were recorded continuously and summed over 5-min epochs. Peak and average activity were defined as the peak and average activity count over all epochs, respectively. Self-reported physical function was measured using the SF36 physical functioning subscale (PF) after completion of the 5-day period. Measures of fatigue (Multidimensional Fatigue Inventory), catastrophizing (Coping Strategies Questionnaire, Catastrophizing subscale), depression (CES-D), anxiety (State-Trait Personality Inventory, Trait Anxiety subscale) and pain (McGill Pain Questionnaire) were also assessed. Data were analyzed using SPSS v.14. Discrepancies between activity (peak and average) and PF scores were calculated as the difference between normalized values, and Pearson's correlation coefficients were obtained among all variables. Simultaneous linear regression models were created to predict peak activity, average activity, and discrepancies between these measures and PF scores; all other variables with significance of correlation < .50 were used as independent variables. Hierarchical regression models were created to check for co-linearity.

Results: SF36 PF scores did not correlate with either peak or average activity ($p = .48$ and .15, respectively). Catastrophizing ($r = .529$, $p < .01$) and fatigue ($r = .521$, $p < .01$) significantly correlated with the degree to which average activity exceeded PF score. Catastrophizing ($r = .404$, $p < .05$) and fatigue ($r = .423$, $p < .05$) also correlated with the degree to which peak activity exceeded PF score. The linear regression model for predicting discrepancy between average activity and PF score was significant ($R^2 = .632$, $p = .002$), and co-linearity was not observed between fatigue and catastrophizing. These discrepancies did not correlate with levels of pain, depression, and anxiety.

Conclusion: Measures of self-reported physical function using the SF36 PF do not correlate with objective measures of activity in FM patients. Higher levels of fatigue and catastrophizing are independently associated with poorer perceived function compared to actigraphy.

Presentation: Significant Association between Changes in Glutamate Levels and fMRI BOLD Signal in the Posterior Insula of Fibromyalgia Patients (2007)

Purpose: Previous functional neuroimaging studies in fibromyalga (FM) patients have shown augmented neural activity within the insula, a region involved in both sensory and affective pain processing. In a recent proton-spectroscopy (H-MRS) study, we found that glutamate (Glu) and/or glutamine levels in the right posterior insula appear to decrease with improvements in multiple pain dimensions within FM patients. These patients had also undergone fMRI as part of the study. We hypothesize that a decrease in fMRI BOLD signal within the right and/or left posterior insula would correlate with these changes in Glu levels, and also with improvements in clinical pain and evoked pain sensitivity.

Methods: As part of an ongoing trial of a non-pharmacological treatment in FM, 10 right-handed female patients (48+/- 15 yrs) underwent both fMRI and H-MRS prior to and following nine treatments. The H-MRS protocol was performed at rest, using single voxel spectroscopy (SVS) with a 2x2x3cm volume of interest placed over the right posterior insula. Using LCModel, levels of Glu were calculated as a ratio to the internal standard creatine (Cre). The fMRI protocol involved two 6.4-minute runs (256 scans each), during which varying amounts of discrete pressure were applied for 25 sec to the left thumbnail in fixed pseudorandom order, alternating with a no-pressure baseline, without producing post-ischemic pain. Images were processed with SPM2. The main effect of interest was the contrast between 0 and 2kg of pressure and how this contrast changed pre- vs. post-treatment. MarsBar was used to extract average BOLD contrast changes in statistically-significant regions of interest within the insula. Clinical and experimental pain were assessed pre- and post-treatment, with the Short Form McGill Pain questionnaire (SF-MPQ) and psychophysical pressure pain testing (multiple random staircase) respectively. Data were analyzed with SPSS v.14.

Results: A positive correlation was found between BOLD contrast changes in the left posterior insula (MNI coordinates {-42, -12, 0}) vs. pre- and post-treatment changes in Glu/Cre in the right posterior insula ($r = 0.801$, $p = 0.005$). Significant positive correlations were also found between these BOLD contrast changes and changes in SF-MPQ sensory ($r = 0.709$, $p = 0.022$) and SF-MPQ total ($r = 0.695$, $p = 0.026$) scores, but not experimental pain sensitivity. No other significant correlations were observed. Conclusion: Changes in pain-induced fMRI BOLD contrast within the left posterior insula over time seem to correlate with changes in clinical pain intensity and varying Glu levels in the right posterior insula. A lack of sufficient statistical power may explain the absence of ipsilateral correlations between fMRI and H-MRS findings.

Differences in regional gray-matter density between fibromyalgia patients and controls: A voxel-based morphometry study

Year: 2008

Poster #: 156

Authors: M Hsu, P Sundgren, R Harris, C Fernandes, R Welsh, D Clauw; University of Michigan, Ann Arbor, MI

Classification: Disease Entities (Human)

Themes: C07 - Myofascial Pain & Fibromyalgia

Description:
Fibromyalgia (FM) is thought to involve abnormalities in central pain processing, and recent studies on small numbers of subjects have suggested reductions in gray-matter density (GMD) in FM patients. Our objective was to search for regional differences in GMD between FM patients and controls, and to determine whether regional GMD is correlated with pressure-pain threshold and symptoms of depression or anxiety. We used a case-control design involving 51 patients and 51 age-matched healthy controls (4% and 10% male, respectively). Our primary outcome measure was regional GMD as estimated by voxel-based morphometry on T1-weighted MRI brain images (1.5mm slice thickness, 3T GE scanner). We excluded scans containing structural lesions or artifacts. We performed a region-of-interest (ROI) search using ROIs based on findings from previous studies, and extracted signal intensities from these ROIs for use in bivariate correlations with pressure-pain threshold (Multiple Random Staircase method), depression (Center for Epidemiological Studies Depression scale) and anxiety (State-Trait Personality Inventory, Trait Anxiety subscale). ROI analysis revealed decreased GMD in the left anterior insula (pFWE=0.051) and right anterior cingulate cortex (pFWE=0.055) in patients compared to controls. No other ROIs showed significant GMD differences between groups. In exploratory analyses we investigated a previously-reported contrast between left and right insula with respect to pain and emotional processing. In patients, the signal intensity difference between left and right insula correlated significantly with depression scores (r=-.374, p=.01). In controls, the signal intensity difference between left and right posterior insula correlated significantly with medium pressure-pain threshold (r=.364, p=.009). This is the largest study to date comparing regional GMD between FM patients and age-matched controls. Subjects with FM seem to exhibit a reduction in GMD in the left anterior insula and right anterior cingulate cortex; decreased density in the left insula relative to right insula seems to correlate with depression in FM.

Presentation: Neuroimaging of Evoked Pain in Individuals with Fibromyalgia and Healthy Controls (ACR/ARHP Annual Scientific Meeting)

Sunday, October 18, 2009: 9:00 AM - 11:00 AM
Hall D (Pennsylvania Convention Center)

Eric Ichesco[1], *Rupal Bhavsar*[1], *Richard Harris*[1], *Daniel Clauw*[2], *Richard Gracely*[3] *and David A. Williams*[1], [1]*U. Michigan, Ann Arbor, MI,* [2]*University of Michigan, Ann Arbor, MI,* [3]*U. North Carolina, Chapel Hill, NC*
Presentation Number: 89
Poster Board Number: 89

Purpose: Prior neuroimaging studies in fibromyalgia (FM) have identified augmented neuronal activity in response to evoked pain when compared to healthy controls (HC). Affected regions are largely contained within the pain matrix (e.g., insula, thalamus, primary and secondary somatosensory cortex, anterior cingulate and the inferior parietal lobe). To date, the majority of the functional magnetic resonance imaging (fMRI) studies in FM have been on a relatively small scale. Heterogeneity within FM as a disease state however suggests the need to replicate earlier findings in a larger sample.

Methods: 57 individuals (mean age 45) satisfying American College of Rheumatology criteria for FM and 20 HC (mean age 42) were studied. During a 10 min fMRI scan, 2 Kg. of pressure (mild pressure) was applied three times to the left thumbnail in random sequence for 25s. A 3-Tesla GE Sigma Scanner with neuro-optimized gradients (FOV = 22cm, T2* weighted, single shot, reverse spinal acquisition, GRE, TR = 2500, TE = 30, FA = 90, 64 x 64) was used to acquire fMRI data. Pre-processing and analysis of BOLD signal was performed using SPM2. Group level T statistical images were generated and uncorrected voxel level threshold of $p<0.002$ was used to identify significant activations.

Results: In FM, 2 Kg. of pressure resulted in significant neural activity in insula (Z = 3.21). bilateral inferior parietal lobes (BA 40, Z = 4.48-4.81), primary somatosensory cortex (Z = 4.03) and secondary somatosensory cortex (Z = 4.69), putamen (Z = 3.27) and caudate (Z = 3.24). Additional activations were observed in the cerebellum (Z = 4.95) and the middle frontal gyrus (Z = 4.37). HC's only had significant activation in the contralateral inferior parietal lobe (BA 40, Z = 3.18) using the same stimulus intensity.

Conclusion: In contrast to HC, mild pressure stimuli resulted in more extensive activation of pain matrix regions in individuals with FM. This study reconfirms an augmented involvement of the "pain matrix" in the processing of evoked pain in FM and supports the role of central mechanisms being responsible for the pain of FM.

Keywords: fibromyalgia, neuroimaging and pain

Disclosure: E. Ichesco, None; **R. Bhavsar**, None; **R. Harris**, Pfizer Inc, 2 ; **D. Clauw**, Forest Laboratories , 2, Pfizer Inc, 2, Cypress Biosciences Inc, 5, Lilly , 5, Pfizer Inc, 5, Forest Laboratories, 5, UCB, 5, Astra-Zeneca, 5, Pierre-Fabre, 5 ; **R. Gracely**, None; **D. A. Williams**, NIAMS-NIH, 2 .

<< Previous Abstract in Session | Next Abstract in Session >>
See more of: Fibromyalgia and Soft Tissue Disorders
See more of: ACR Poster Sessions

Presentation: Persistent Musculoskeletal Pain and Posttraumatic Stress Disorder Symptoms After Motor Vehicle Collision Share ED Symptom Risk Factors and Outcomes (2006)

C.W. Jones, S.A. McLean, M.R. Sochor, C.R. Newton, A.D. Withrow, J. Fowler, B.A. Stanislawski, D.A. Williams, I. Liberzon, D.J. Clauw,

Purpose: Chronic musculoskeletal pain is common after motor vehicle collision (MVC), but the etiology remains poorly understood. It has been proposed that stress system dysregulation may contribute to the development of both chronic pain and psychological sequelae such as posttraumatic stress disorder (PTSD) after MVC. However, little data is available regarding shared risk factors and outcomes for these disorders.

Material and Methods: Patients being evaluated in the emergency department (ED) after MVC were recruited into an ongoing multicenter study which includes ED baseline assessment and 1-month follow-up evaluation. ED evaluation includes an assessment of post-MVC symptoms such as neck pain, sense of life threat during the collision, and participant completion of the Peritraumatic Distress Scale, a known predictor of PTSD. One month telephone follow-up evaluation assessed the presence of MVC-related neck or back pain symptoms and PTSD symptoms (IES-R). Moderate or severe pain at 1 month was defined by a numeric rating scale score of ≥ 4 on a 0-10 numeric rating scale. Significant PTSD Symptoms were defined by IES-R score ≥ 33. Pain and PTSD outcomes were compared, and correlations between baseline risk factors and 1-month outcomes were calculated.

Results: To date, follow-up data has been obtained in 48 of 49 enrolled patients who have reached the 1-month follow-up time point (98%, 28 female, 20 male, age 18-84, mean 36.4 years). Twelve (21%) reported persistent moderate or severe MVC-related neck pain, 17 (31%) reported moderate or severe MVC-related back pain, 11 (24%) reported significant PTSD symptoms. Persistent MVC-related neck and back pain symptoms were strongly associated with persistent PTSD symptoms ($r = .505$, $p = .000$). Interestingly, ED neck pain score was more strongly associated with 1-month PTSD symptoms ($r = 347$, $p = .016$) than ED Peritraumatic Distress Scale score ($r = .333$, $p = .021$), a known predictor of PTSD.

Conclusion: These pilot data suggest that PTSD and chronic pain symptoms after MVC are frequently co-morbid, and that ED pain symptoms are a strong risk factor for both disorders. Updated information from this ongoing trial will be presented at the meeting.

Presentation: Pain and Fatigue Symptoms in Healthy Individuals after Sleep and/or Exercise Restriction (2006)

Introduction. Regular exercise and "good" sleep are salubrious mainstays of overall well-being, regardless of disease state. Despite evidence that sleep hygiene and regular exercise can help manage fibromyalgia symptoms, many find it difficult to incorporate such behaviors into their routine. We speculate that an absence of these behaviors can contribute to exacerbated symptoms, and even acute symptom development among non-patients, and hypothesize that some healthy individuals are prone to fibromyalgia-like symptoms because exposure to a "stressor" (e.g. acute musculoskeletal pain, infection, etc.) causes them to modify their sleep and exercise routines.

Methods. We recruited 36 healthy adults (18-41 yrs) as part of an ongoing exercise and sleep deprivation study. Eligibility required a minimum of 5 days/week and 20 miles (or 4 hr) of running and at least 7-9 hrs sleep/night. Subjects were randomly assigned to one of four groups: control (normal activity and sleep), exercise deprivation, sleep restriction (6 contiguous hours in bed per night), or both exercise and sleep restriction. Each deprivation phase lasted 10 days. We assessed symptom development in 4 domains (pain, mood, fatigue, and cognition) at baseline and between days 7-8 of the deprivation period. Sleep and exercise were entered into a 2-way ANOVA with various symptom outcomes as the dependent variable to evaluate the main effects and interactions of each deprivation category.

Results. There was a significant main effect for sleep on self-report measures across all four symptom domains. Representative measures are reported: Pain (McGill Total Score: $F(1,34)=5.11$, $p<0.05$); Fatigue (POMS Fatigue Scale: $F(1,34)=27.99$, $p<0.0001$); Mood (CES-Depression: $F(1,34)=12.86$, $p<.001$); and Cognition (MASQ- Attention/ Concentration: $F(1,34)=5.59$, $p<.001$). Exercise elicited a non-significant main effect across these same measures ($p>0.05$), and there were no significant interactions ($p>0.05$). Exercise restriction alone had a marginal effect in this sample, though it tended to augment symptom experience with sleep restriction.

Conclusions. Amongst healthy individuals, a subset is prone to acute symptom development following disruption to their normal routine, with the general trend thus far suggesting that a combined sleep/exercise restriction elicits the highest level of symptom increase, followed by sleep restriction alone, and lastly exercise restriction alone.

Presentation: Emergency Department Physiologic Predictors of Pain and Psychological Sequelae After Motor Vehicle Collision (2006)

S.A. McLean, M. Switzer, C.W. Jones, M.R. Sochor, C.R. Newton, A.D. Withrow, J. Fowler, D.A. Williams, P.K. Stein, I. Liberzon, D.J. Clauw,

Purpose: It has been proposed that stress system dysregulation may contribute to the development of both chronic pain and psychological sequelae after motor vehicle collision (MVC). However, the association between emergency department (ED) cortisol levels and high frequency heart rate variability (HF HRV, representing parasympathetic function) and these sequelae has not previously been examined.

Material and Methods: Patients being evaluated in the ED after MVC were recruited into an ongoing multicenter study which includes ED baseline assessment and 1-month outcome evaluation. ED assessment includes salivary cortisol collection and 20 minute Holter monitor recording. Outcome evaluation includes assessment of persistent moderate or severe MVC-related neck or back pain symptoms (numeric rating scale score of ≥ 4 [0-10 scale]), significant PTSD symptoms (IES-R score ≥ 33), and significant depressive symptoms (CES-D ≥ 27). Cortisol samples were assayed using the Diagnostic Products Corporation Coat-a-Count cortisol kits. HF HRV was assessed using HF power spectral analysis (0.15 to 0.4-Hz). Associations between ED cortisol and HF HRV and 1 month outcomes were assessed via ANOVA and t-tests.

Results: To date, follow-up data has been obtained in 48 of 49 enrolled patients who have reached the 1 month follow-up time point (98%, 28 female, 20 male, age 18-84, mean 36.4 years). ED cortisol and HF HRV levels were associated with 1 month outcome (Tables 1 and 2).

Conclusion: These pilot data suggest that physiologic characteristics of patients assessed in the ED are associated with post-MVC pain and psychological sequelae. These characteristics may assist in the identification of individuals at high risk of pain and psychological sequelae, and may provide new insights into the pathophysiology of these disorders. Updated information from this ongoing trial will be presented at the meeting.

Presentation: Altered Temporal Sequences of Evoked Brain Activity in Fibromyalgia (2006)

R. Patel, R.H. Gracely, G.A. Naylor, B.K. Michalik, L.M. Skalski, D.J. Clauw,

Introduction: fMRI studies of fibromyalgia (FM) have showed augmented pain processing to pressure and heat. This study used brief (5s) painful pressure stimuli and the high temporal resolution of fMRI to assess the sequence of pain-evoked brain activity in healthy controls (HC) and compare this sequence to that observed in FM.

Methods: Twenty female patients (mean age = 45) satisfying ACR criteria for FM and 20 matched HC (mean age = 45) participated in the study. Before fMRI scanning, the effects of painful pressure applied to the left thumbnail were assessed using the Multiple Random Staircase method and a verbal-numerical Box pain scale to determine stimulus pressures sufficient to evoke subjective levels of mild, moderate or intense pain sensations. During 10 min fMRI scans, these pressures were applied to the thumbnail in random sequence during 5s of painful pressure presented at 25 s intervals. fMRI data were acquired by a 3 Tesla scanner every 2.5 s (TR 2.5s, TE 30 ms, FA 90, 64x64 matrix, 48 horizontal slices; spiral acquisition). Analysis of the BOLD signal (head motion correction, slice timing corrections, spatial smoothed 6mm FWHM, intensity normalization, conversion to standard coordinate system, and modeling to an expected haemodymanic response was performed using Medx.

Results: The temporal response was classified as [E]arly, [M]iddle or [L]ate (E = 2.5 sec, M = 5 sec, L = 7.5 sec of haemodynamic lag).

Region	**HC:** Early	Middle	Late	**FM:** Early	Middle	Late
Anterior Cingular Cortex (ACC)	*		*			
Cerebellum	*		*		*	*
Thalamus	*	*			*	
Inferior Parietal Lobule (IPL)	*	*			*	
Inferior Frontal Gyrus (IFG)	*	*	*			
Medial Frontal Gyrus (MFG)		*	*		*	
Insula			*			
Basal Ganglia			*		*	
Brainstem			*			
Claustrum					*	

Conclusion: In HC, brief pressure stimuli evoked immediate responses (Thalamus, Cerebellum, ACC, IPL, IFG) and late responses (IFG, MFG, Insula, Brainstem) that were not observed in FM. This delayed and shortened response in FM contrasts with augmentation observed with longer (25-30s) pressure stimuli, suggesting a tonic inhibitory state that during prolonged stimulation is quickly attenuated, and/or opposed by facilitatory mechanisms.

Presentation: Stimulation Duration Alters the Initial fMRI Response to Painful Pressure in Fibromyalgia and Healthy Contols (2006)

R. Patel, **B.K. Michalik**, **L.M. Skalski**, **D.J. Clauw, R.H. Gracely**,

Introduction: Neuroimaging studies of pain processing usually deliver brief (e.g. 5s) stimuli. fMRI studies of fibromyalgia (FM) have shown augmented pain processing to pressure stimuli of 25-30s duration. To investigate further differences in pain processing in FM, this study compared the initial effects of brief 5s painful pressure stimuli and the first 5s of a 25s stimulus. The analysis evaluated if these identical stimulus conditions are influenced by subsequent stimulus duration during a scanning session in healthy control subjects (HC) and the impact of this effect on pain processing in FM.

Methods: Twenty female patients satisfying ACR criteria for FM and 20 age-matched HC participated in two sessions. Before fMRI scanning, a psychophysical staircase method was used to determine stimulus pressures that evoked slightly intense pain. During 10 min fMRI scans, these pressures were applied to the left thumbnail in random sequence during either 5s of painful pressure presented at 25s intervals or 25s of pressure presented at 50s intervals. fMRI data were acquired by a GE 3 Tesla scanner every 2.5s and analysis of the BOLD signal was performed using Medx (convoluted 5s box car with 2.5s haemodynamic delay). The analysis evaluated the first 5s of stimulation in each condition, which included the entire 5s stimulus and the first 5s of a 25s (5/25s) stimulus.

Results: During equally painful slightly intense stimulation in HC, the 5/25s stimulus evoked unique early activity in bilateral cerebellum (Z= 4.91-5.85), middle frontal gyrus (BA6, 10; Z=3.26-3.73) and ipsilateral hippocampus (Z=3.90). In contrast, the 5s stimulus evoked unique early activity in contralateral thalamic medial dorsal nucleus (MDN, Z=5.16) and bilateral anterior nuclei (Z=3.32-3.60). Additional unique activations were observed in contralateral anterior cingulate cortex (ACC, Z=4.83-5.08), inferior parietal lobule (Z=3.95) and midbrain (Z=4.27). These effects of method were not observed in FM. The 5/25s stimulus evoked unique activations in the contralateral inferior frontal (BA 45, 47; Z=4.13-5.03) and middle frontal (BA 45, 46; Z=3.79-3.80) gyri and in ipsilateral brainstem (Pons, Z=3.81). The 5s stimulus evoked no early activity in FM.

Conclusion: HC response to 5s of stimulation was influenced by the subsequent duration of the stimulus, which may involve somatic mechanisms of sensitization and intrinsic inhibition and psychological mechanisms of anticipation and conditioned responses to stimulation. FM showed a different pattern of responses to the early part of the prolonged stimulus and no effects to the 5s stimulus. This result provided further evidence of altered pain processing in FM and suggests a method that examines temporal patterns rather than magnitude of evoked activity.

Presentation: Functional MRI (fMRI) of Pain Processing is Stable over Time in Fibromyalgia (FM) Patients without Changes in Clinical Status (2007)

R. Patel, **D.A. Williams**, **R.H. Gracely, L. Skalski**, **S.J. Chriscinske**, **G. Alesi**, **D.J. Clauw**,

Purpose: Neuroimaging studies using painful stimuli have been helpful in identifying brain regions associated with augmented sensory and affective characteristics of pain processing in patients with FM. To date, these studies have examined FM patients at single points in time. We are not aware of any study that has performed fMRI of pain processing at two separate points in time in patients with FM, to look for stability of fMRI findings over time. Showing such stability would be helpful in establishing that fMRI might serve as a valid biomarker in FM and related conditions.

Methods: 9 female patients (mean age = 45) satisfying ACR criteria for FM were selected from a larger pre-existing dataset based on very little to no change from 0-12 week in clinical pain, using the Brief Pain Inventory (BPI). After each assessment with the BPI, each participant underwent standardized evoked pressure pain testing (EPP) and fMRI neuroimaging. During 10 minute fMRI sessions, pressures calibrated to evoke mild, moderate, and slightly intense pain were applied to the left thumb by a 1cm diameter probe, as was 2kg of pressure for all participants (the scans used for this study). Identical methods were used at both sessions. fMRI data were acquired by a GE3 Tesla scanner at 2.5s intervals. Analysis of the BOLD signal (head motion correction, slice timing correction, spatial smoothed 6mm FWHM, intensity normalization, conversion to standard coordinate system, statistical comparison of 2kg response at 12 weeks to baseline) was performed using Medx.

Results: During equal pressure conditions, patients who showed no change in clinical pain also showed no significant differences in fMRI results from baseline to 12 weeks. There were mild changes in several regions over time but none approached the corrected Z threshold of 3.64.

Conclusions: This study suggests that even over fairly long periods of time, fMRI of pain processing is relatively stable in FM patients in whom there is no significant change in clinical symptoms. Such stability over time is a desirable attribute of a biomarker.

Differences in Central Neural Pain Processing Following Acupuncture and Sham Acupuncture Therapy in Fibromyalgia (FM)

Ann A. Poznanski, Michael Hsu, Richard H. Gracely, Daniel J. Clauw, and Richard E. Harris

Clinical trials of acupuncture for the trea tment of chronic pain conditions such as fibromyalgia (FM) have resulted in equivo cal findings. In m ost studies, traditional acupuncture and sha m acupuncture are equally effective. However no study has used functional magnetic resonance im aging (fMRI) in FM pa tients to exam ine more detailed changes in central p ain proces sing follo wing trad itional and sham acupuncture. 25 female FM participan ts were ran domized to receiv e either 9 sessions of traditiona l Chinese acupuncture (T A; n =13; m ean(SD)age=48.9(11.3)yrs) or 9 sessions of sha m acupuncture (SA; n=12; m ean(sd)age=42.9(13.6)yrs) over the course of one month. Neural activity evoked by painful pressures applied to the thum bnail was assessed pre- and post- treatment with f MRI. Clinical p ain was assesse d with the Short Form of the McGill Pain Questionn aire (SFMP Q) and exp erimental p ressure pain sensitiv ity was assessed pre- and post-treatm ent. The entire cohort displayed reductions in both clinical and experim ental pain (SFMPQ total mean(SD)change=5.15(5.65), p=0.001; m ild pressure pain threshold m ean(SD)change kg=0.58(0.85), p=0.003), however no significant differences in the am ount of pain reduction were detected between groups for either pain dim ension (both p>0.15). Signi ficant differences in pain evoked neural activity were detected between T A and SA for the inferior parietal lobule (Z =3.5; p<0.001 uncorrected) and two regions in the cerebellum (region 1: Z=3.08; p=0.001 uncorrected; region 2: Z =3.2; p<0.001 uncorrected). In these regions greater reductions in pain evoked activity were detected following TA. Other regions within the cerebellum and the posterior cingulate showed trend s tow ards great er reductions following TA (p<0.002 uncorrected). No regions were det ected that showed greater reductions in neural activity following SA. Although both TA and SA resulted in similar reductions in pain repo rt, f MRI was able to d etect dif ferences between these tw o treatm ents. fMRI may more sensitive at detecting changes in pain processing than subjective pain report.

Funding:
Department of Army grant DAMD-17/002-0018
NIH/NCRR grant M01-RR000042 and NIH/NCCAM K01 AT01111-01 awarded to REH.

Central μ-Opioid Receptor (MOR) Availability Covaries with Mood State and Pain in Fibromyalgia (FM)

Year: 2008

Poster #: 155

Authors: Y Qiu, J Zubieta, D Scott, R Gracely, D Clauw, R Harris; The University of Michigan, Ann Arbor, MI

Classification: Disease Entities (Human)

Themes: C07 - Myofascial Pain & Fibromyalgia

Description:
Fibromyalgia (FM) is a chronic widespread pain condition that is often accompanied by comorbid negative mood states including stress and depression. Positron emission tomography (PET) studies have demonstrated alterations in central μ-opioid receptor (MOR) availability in fibromyalgia patients as well as patients diagnosed with major depressive disorder. However, the regulation of the endogenous opioid system in the experience of negative mood states and pain within the same individuals is less well understood. Using PET to label MORs, we examined the correlation between the availability of MORs in the brain and self reported mood and pain in 20 fibromyalgia patients (49.5 (13.2) yrs). Mood and pain were assessed by the Positive and Negative Affectivity Scale (PANAS) and the Short Form of the McGill Pain questionnaire respectively. Negative affect was positively correlated with MOR binding potential (BP; an in vivo measure of receptor availability) in anterior cingulate cortex (ACC: $r=0.77;p<0.001$), middle-posterior insula ($r=0.67;p=0.001$), hippocampus ($r=0.67;p=0.001$) and dorsolateral prefrontal cortex ($r=0.75;p<0.001$). Within these regions, clinical pain was positively correlated with MOR BP only in the ACC ($r=0.58;p<0.01$) and middle-posterior insula ($r=0.56;p=0.01$). Linear regression analyses demonstrated that MOR BP (availability) in the ACC was independently correlated with both negative affect (Beta 0.64; $p<0.001$) and pain (Beta 0.33; $p=0.04$). These data support a model in which reduced endogenous opioid release is associated with pain and negative affect in FM patients albeit in partially overlapping brain regions. Funding: Department of Army grant DAMD-17/002-0018. NIH/NCRR grant M01-RR000042, NIH/NCCAM grant R01 AT 001415 awarded to JKZ, and NIH/NCCAM K01 AT01111-01 awarded to REH.

Presentation: Characteristics Associated with Neck Pain Persistence versus Recovery after Minor Motor Vehicle Collision (2007)

D. Robinson, S.A. McLean, R. Swor, E.M. Zaleski, Y. Mistry, S. S, M.R. Sochor, C. Newton, I. Liberzon, D.J. Clauw,

Purpose: Persistent musculoskeletal neck pain is common after minor motor vehicle collision (MVC). Little is known regarding characteristics that distinguish individuals who experience musculoskeletal neck pain symptom resolution versus persistence. We sought to compare individuals with neck pain symptoms in the emergency department (ED) who did and did not have persistent musculoskeletal neck pain 1 month after MVC.

Material and Methods: Patients being evaluated in the emergency department (ED) after MVC were recruited into an ongoing multicenter study that includes ED baseline assessment and 1 month follow-up evaluation. ED evaluation includes an assessment of demographic, health, psychological, and symptom factors. One month telephone follow-up evaluation includes an assessment of MVC-related neck pain. Those reporting neck pain severity ≥ 4 on a 0-10 numeric rating scale were defined as having moderate or severe pain. Descriptive analyses were used to compare individuals with initial neck pain symptoms with and without persistent moderate or severe neck pain.

Results: Of 126 enrolled patients evaluated to date at the 1 month time point, 41 (33%) had initial neck pain in the ED but no moderate or severe neck pain at 1 month, and 47 (37%) had initial neck pain in the ED and persistent moderate or severe neck pain. Table 1 displays characteristics that distinguished these two groups.

Conclusion: Demographic, symptom, and cognitive characteristics distinguish patients in whom initial neck pain symptoms do and do not resolve. More work is needed to understand the pathophysiology of neck pain persistence vs. recovery after MVC.

Table 1: Characteristics of those with Neck Pain Persistence vs. Recovery after Minor Motor Vehicle Collision

Characteristic	Recovered (n = 41)	Persistence (n = 47)	t (p) or χ^2 (p)
Age (years)	34.7 (13.6)	43.7 (15.2)	2.91 (.005)
Income ≤ $20,000	23%	37%	9.55 (.089)
Pre-MVC Depressive Symptoms (CES-D)	11.4 (9.8)	16.2 (13.7)	1.82 (.073)
Pre-MVC Anxiety Symptoms (STPI)	20.6 (2.0)	22.2 (4.0)	2.27 (.027)

ED Neck Pain Intensity	4.6 (2.0)	6.5 (2.1)	4.23 (<.0001)
Peritraumatic Distress (Peritraumatic Distress Scale)	19.6 (2.0)	23.8 (9.2)	2.08 (.041)
Research assistant rating of patient distress (initial rating)	1.6 (1.4)	3.0 (2.6)	3.03 (.003)
Patient certainty that they will recover (initial rating)	9.6 (.69)	8.4 (2.0)	3.80 (<.0001)
Feeling that the accident was another person's fault	65%	74%	3.15 (.207)

Presentation: Predictors of Persistent Moderate or Severe Neck and/or Back Pain 1 and 6 Months after Minor Motor Vehicle Collision (2007)

S. Schon, S.A. McLean, Y. Mistry, E.M. Zaleski, R. Swor, D. Robinson, M.R. Sochor, C. Newton, I. Liberzon, D.J. Clauw,

Purpose: Chronic musculoskeletal neck and back pain is common after motor vehicle collision (MVC), but the etiology remains poorly understood. The relative predictive utility of demographic, psychological, physiological, and initial symptom factors is not known.

Material and Methods: Patients being evaluated in the emergency department (ED) after MVC were recruited into an ongoing multicenter study that includes ED baseline assessment and 1 and 6 month follow-up evaluation. ED evaluation includes an assessment of demographic, health, psychological, symptom, and physiologic factors. One and 6 month telephone follow-up evaluation assessed the presence of MVC-related moderate or severe pain symptoms (≥ 4 on a 0-10 numeric rating scale) in the neck and/or back. The best combination of predictive factors for moderate or severe neck and/or back pain at each follow-up point was selected via stepwise logistic regression modeling. Model utility was evaluated via receiver operating characteristic (ROC) curve analyses.

Results: To date, 1 month follow-up data is available on 126 participants, and 6 month follow-up data is available on 69. The optimal set of 1 month predictors were age, race, pre-MVC anxiety symptoms, intensity of neck pain in the ED, and heart rate divided by systolic blood pressure (a measure of baroreceptor function, which is associated with neurosensory processing). The optimal set of 6 month predictors were somatic symptoms prior to the ED visit, general health, dissociative symptoms at the time of the MVC, initial patient estimate of the time until physical recovery, and initial neck pain symptoms. ROC curves for these models are shown in figure 1.

Conclusion: These pilot data suggest that a relatively small number of baseline predictors provides excellent prediction of persistent musculoskeletal pain after MVC.

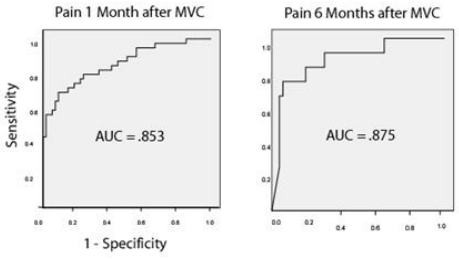


Figure 1

Presentation: Increased mu-Opioid Receptor Availability is Detected During Clinical Pain Reduction in Fibromylagia Patients (2006)

D.J. Scott, **R.E. Harris**, **G.A. Naylor**, **J.B. Romond**, **A.R. Bradford**, **R.H. Gracely**, **D.J. Clauw**, **J. Zubieta**,.

Purpose: Fibromyalgia involves chronic, widespread idiopathic pain, yet the biological mechanisms underlying this disease remain poorly understood. As endogenous opioids play a key role in modulating pain perception, we investigated the role of mu-opioid receptor (MOR) activity in fibromyalgia patients.

Methods: 11 female patients diagnosed with fibromyalgia were examined using positron emission tomography (PET) and [^{11}C]carfentanil, a MOR selective radiotracer. Patients met ACR 1990 criteria for the diagnosis of fibromyalgia for at least 1 year. During the scanning session patients underwent one acupuncture or one sham acupuncture intervention. For the purpose of this analysis, data from both groups were combined. Pain report was recorded immediately before and after the intervention using GBSintensity, GBSunpleasantness, and a Visual Analog Scale (VAS). Logan plots were created to obtain maps of whole-brain MOR binding potential (BP) at baseline and following the intervention. Changes in opioid binding between conditions were assessed using SPM99, and regions showing significant differences in BP were extracted using locally developed software. Correlations between pain report and MOR occupancy were performed in SPSS.

Results: Following the intervention, patients reported significantly reduced clinical pain as measured by all three scales (GBSintensity: $p = .001$; GBSunpleasantness: $p = .02$; VAS rating: $p < 0.02$). Patients also showed significantly increased ($p < 0.0005$) MOR availability in the left nucleus accumbens ($z = 9.0$) and amygdala bilaterally (left, $z = 10.1$; right, $z = 9.8$) following the intervention. The percent increase in MOR occupancy within the nucleus accumbens was significantly correlated with reductions in all clinical measures (GBSintensity: $r = 0.60$, $p = 0.05$; GBSunpleasantness: $r = 0.84$, $p = 0.001$; VAS: $r = 0.73$, $p = 0.01$).

Conclusions: We report that increased MOR availability is associated with improved pain report in fibromyalgia patients. These results implicate short-term modulation of this analgesic system in chronic pain reduction. As such, the endogenous opioid system may play a role in future trials investigating fibromyalgia.

Presentation: Pre-MVC Symptom and Psychological Characteristics are Associated with Persistent Pain and Psychological Symptoms after MVC (2006)

M. Switzer,; S.A. McLean, C.W. Jones, M.R. Sochor, C.R. Newton, A.D. Withrow, J. Fowler, D.A. Williams, I. Liberzon, D.J. Clauw,

Purpose: Chronic musculoskeletal pain and psychological sequelae are common after motor vehicle collision (MVC), but the etiology of these disorders are not well understood. Somatic symptoms and psychological factors are identified risk factors for chronic pain and psychological disorder development in other settings, but the relative influence of these factors on post-MVC outcomes has not previously been examined.

Material and Methods: Patients being evaluated in the emergency department (ED) after MVC were recruited into an ongoing multicenter study which includes ED baseline assessment and 1-month outcome evaluation. ED evaluation included an assessment of somatic symptoms, depressive symptoms (CES-D), anxiety symptoms (STPI), and perceived stress (Cohen) in the calendar month prior to the MVC. One-month outcome assessment includes evaluation of persistent MVC-related neck or back pain symptoms, PTSD symptoms (IES-R), and depressive symptoms (CES-D). Associations between baseline psychological and somatic symptoms and 1-month outcomes were assessed via correlation analyses.

Results: To date, follow-up data has been obtained in 48 of 49 enrolled patients who have reached the 1-month follow-up time point (98%, 28 female, 20 male, age 18-84, mean 36.4 years). Comparison of baseline symptom and psychological factors and 1-month outcomes are shown in Table 1. Baseline somatic symptoms were strong predictors of both 1-month pain and psychological sequelae of MVC. Baseline anxiety and depressive symptoms and perceived stress were strong predictors of psychological outcomes but not pain outcomes.

Conclusion: These pilot data suggest that somatic symptoms are strong predictors of MVC-related pain and psychological sequelae. Baseline psychological factors appear to be strong predictors of psychological sequelae but may be less predictive of chronic MVC-related pain. Updated information from this ongoing trial will be presented at the meeting.

Table 1. Association between pre-MVC psychological symptoms and early and persistent pain an psychological sequelae 1 month after MVC

Pre-MVC psychological factor	**Mood Outcomes**		**PTSD Outcomes**	**Pain Outcomes**
	Mood Interference 3-7 days after MVC	Depressive Symptoms 1 month after MVC	PTSD Symptoms[1] 1 Month after MVC	Pain Symptoms[2] Month after MVC
Somatic[3] symptoms	.350 (.025)	.519 (.000)	.444 (.002)	.363 (.014)
Anxiety[4] Symptoms	.278 (.079)	.469 (.002)	.418 (.005)	-.061 (694)

Perceived[5] Stress	.119 (.448)	.266(.085)	.072 (.636)	-128 (.395)
Depressive[6] Symptoms	.126 (.457)	.461 (.004)	.268 (.103)	-.100 (.546)

[1]IES-R, [2]Sum of MVC-related neck or back pain (0-20 NRS), [3]Symptoms listed in text, [4]STPI, [5]Cohen Perceived Stress Scale, [6]CES-D

Presentation: Improving Internal Locus of Pain Control in Fibromyalgia (ACR/ARHP Annual Scientific Meeting)

Tuesday, October 20, 2009: 9:00 AM - 11:00 AM
Hall D (Pennsylvania Convention Center)

David A. Williams[1], *Kirsten Ambrose*[2], *Linda Skalski*[3], *Jordana Muroff*[4], *Lynn Zwinck*[1] *and Daniel Clauw*[5], [1]*U. Michigan, Ann Arbor, MI,* [2]*Algynomics, Inc., Chapel Hill, NC,* [3]*Duke University, Durham, NC,* [4]*Boston University, Boston, MA,* [5]*University of Michigan, Ann Arbor, MI*
Presentation Number: 1418
Poster Board Number: 151

Purpose: Interventions for pain typically target sensory (e.g. nociceptive) or affective aspects of pain with little to no emphasis on altering cognitive aspects of pain. One cognitive factor, “a perceived ability to control pain” holds clinical relevance across many pain conditions. An internal locus of pain control (I-loc) refers to a belief in pain being an experience that can be modified through personal effort. Actual life experiences may support such beliefs (e.g., success in using behavioral coping skills for pain). An external locus of control such as believing that powerful doctors (PD-loc) or chance events (C-loc) control the experience of pain are more common among individuals with pain. For many diseases including chronic pain, possession of a strong (I-loc) is associated with better outcomes. This study sought to improve (I-loc) in a sample of individuals with FM.

Method: 72 females satisfying ACR criteria for FM (mean age=45.5, (SD=9.9)) were randomly assigned to one of three treatment arms: Exercise (exc), Relaxation (rlx), or standard care (std). Manualized exercise or relaxation sessions consisted of 1 face-to-face session with a therapist who followed patients by scheduled telephone contact over 8 weeks. Baseline and 12-week endpoint evaluations included the following: the Beliefs in Pain Control Questionnaire (BPCQ), the Brief Pain Inventory, and the SF-36. Within subject and between group comparisons were made using ANCOVA with the baseline value of the dependent variable serving as the covariate. Responders to treatment were defined as individuals demonstrating a minimal clinically important difference on I-loc (i.e., improving >=0.5 SD).

Results: While no differences existed between groups at baseline, ANCOVA revealed significant group differences in (I-loc) at post treatment $F_{(2,68)}=3.14$, $p<.05$. I-loc was significantly more improved for the exercise arm than for std care but not different from the relaxation arm. Responders were identified in each arm at differing rates: std: 17%; exc: 42%; rlx: 33%. In comparisons of responders with non-responders from any treatment, ANCOVAs revealed that even though pain severity was not different, I-loc responders had significant reductions in the number of painful body regions ($F_{(1,69)}=4.53$, $p<.05$) at post treatment.. Responders also demonstrated significant improvements in physical functional status as assessed by the SF-36 PCS score ($F_{(1,69)}=6.55$, $p<.01$). Improvement in I-loc was not associated with change on any of the indices of affect.

Conclusion: I-loc, a belief in personal pain control, is modifiable through brief non-pharmacological approaches such as exercise and relaxation. Bolstering the belief in I-loc appears to influence pain by influencing perceptions of illness impact rather than symptom severity in individuals with FM.

Presentation: Cognitive Dysfunction in Fibromyalgia Assessed by the Multiple Abilities Self-Report Questionnaire (ACR/ARHP Annual Scientific Meeting)

Tuesday, October 20, 2009: 9:00 AM - 11:00 AM
Hall D (Pennsylvania Convention Center)

David A. Williams[1], *Jennifer M. Glass*[1], *Paloma Barjola*[2], *Lynn Zwinck*[1] *and Daniel Clauw*[3], [1]*U. Michigan, Ann Arbor, MI,* [2]*Rey Juan Carlos University, Madrid, Spain,* [3]*University of Michigan, Ann Arbor, MI*
Presentation Number: 1417
Poster Board Number: 150

Purpose: Individuals with fibromyalgia (FM) often report cognitive difficulties (a.k.a., “fibro-fog”). Studying fibro-fog has been difficult due to several factors: (a) incongruence between objective (i.e., neuropsychological) assessment and self-report, and (b) the inconsistent manifestation of cognitive difficulties across individuals with FM. The current study sought to (a) assess multiple cognitive difficulties within individuals, (b) compare cognitive difficulties in FM with healthy controls (HC)’s, and (c) identify clinical correlates for the various types of cognitive problems. To date, fibro-fog has been hypothesized to be associated with a wide variety of clinical problems (e.g. pain, sleep loss, fatigue, mood etc.).

Method: 101 individuals meeting American College of Rheumatology criteria for FM were compared to 63 HC’s. All participants completed the Multiple Abilities Self-report Questionnaire (MASQ), a measure of perceived cognitive difficulties with language, Visual-perception, verbal memory, visual-spatial memory, and attention/concentration. Multiple Analysis Of Variance (MANOVA) was used to compare the MASQ scales between FM and HC. The following clinical correlates of fibro-fog were assessed: age, pain severity (Brief Pain Inventory, (BPI)), fatigue (physical and mental scales of the Multidimensional Fatigue Inventory, (MFI)), sleep problems (MOS sleep index 1), stress (Perceived Stress Scale, (PSS)), trait anxiety and depression (State-Trait Personality Inventory, (STPI). For individuals with FM, correlations were obtained for the MASQ scales and each clinical variable. Clinical variables having significant first order correlations with the MASQ scales were then used in stepwise regression models so as to identify significant and unique clinical contributors to each of the MASQ scales.

Results: MANOVA revealed significant differences between FM and HC on all MASQ scales (Wilk’s Lambda=.070, $p<.0001$.). Language problems were significantly associated with physical and mental fatigue, stress, and trait depression. The strongest predictor of language problems was mental fatigue accounting for 16% of the variance. Problems with visual perception were only significantly correlated with stress accounting for 8% of the variance. Verbal memory difficulties were associated with mental fatigue, stress, and trait anxiety. Together, mental fatigue and stress accounted for 45% of the variance. Visual-spatial memory was associated with age, trait depression, and stress. Stress accounted for greatest amount of variance (12%). Attention/concentration was associated with physical and mental fatigue and trait depression; all three made unique and significant contributions accounting for 24% of the variance.

Conclusion: The MASQ is an assessment tool that can capture multiple dimensions of fibrofog which appear to be related to differing constellations of underlying clinical factors.

Presentation: Functional MRI (fMRI) Appears to Act as a Biomarker in Fibromyalgia (FM) by Identifying Neurobiological Correlates of Changes in Pain Over Time (2007)

D.A. Williams, **R. Patel**, **L. Skalski**, **S.J. Chriscinske**, **M. Rubens**, **J. Lapedis**, **R.E. Harris**, **R.H. Gracely**, **D.J. Clauw**,

Purpose: Previous fMRI studies using both pressure and heat stimuli have shown that FM is characterized by augmented central pain processing. To summarize, these studies have shown that with equal amounts of stimuli to controls, FM is characterized by augmented neuronal activity in regions of the brain associated with processing both sensory and affective stimuli. To date, these studies have been cross-sectional, and identified differences between patients and controls. The current study performed fMRI both before and after a behavioral intervention for FM, and compared neuronal activation patterns at baseline and post-treatment in a group with worsening clinical pain and a group that improved.

Methods: 18 female patients satisfying ACR criteria for FM were selected from a larger preexisting dataset based upon either improving or declining 0-12 week change scores in the Brief Pain Inventory (BPI). Group A had 12 patients (mean age = 45) with improvements in pain severity (1.92 U) and group B had 7 patients (mean age = 48) with worsening severity (1.93 U). After each assessment with the BPI, participants underwent standardized evoked pressure pain testing (EPP) and fMRI neuroimaging. During 10 minute fMRI sessions, pressures calibrated to evoke mild, moderate, and slightly intense pain were applied to the left thumb by a 1 cm diameter probe, as was 2kg of pressure for all participants (the scans used for this study). Identical methods were used at both sessions. fMRI data were acquired by a GE 3 Tesla scanner at 2.5s intervals and analysis of the BOLD signal was performed using Medx, correcting for multiple comparisons, using a region of interest analysis. Baseline activation data was subtracted from the 3-month data revealing regions of increased or decreased activity in response to identical stimuli over time.

Results: During equal pressure conditions, patients who showed *decreased* clinical pain severity, also showed significant *decreased* BOLD activity in brainstem, caudate, thalamus, putamen, inferior parietal lobule (BA 40), secondary somatosensory cortex, anterior cingulate cortex (BA 32 and BA 24), medial frontal gyrus (BA 6), and increased activity in only in the primary somatosensory cortex and middle frontal gyrus (BA 10). Patients whose pain *worsened* showed significant *increased* activity in insula, brainstem regions, inferior parietal lobule (BA40), middle frontal gyrus (BA 10) and decreased activity only in the middle frontal gyrus (BA 6).

Conclusions: These data suggest that increases or decreases in clinical pain in FM are associated with corresponding changes in neuronal activation patterns in brain regions involved in pain processing. These data suggest that fMRI may be able to serve as a biomarker in FM.

Presentation: Cognitive and Behavioral Factors Assessed 3-7 Days after Motor Vehicle Collision are Associated with Persistent Pain and Psychological Symptoms (2006)

A.D. Withrow, S.A. McLean, M.R. Sochor, C.R. Newton, M. Switzer, J. Fowler, D.J. Clauw, D.A. Williams,

Purpose: Chronic musculoskeletal pain and psychological sequelae are common after MVC, but the etiology of these disorders are not well understood. Cognitive and behavioral factors following MVC are suspected to contribute to the development of persistent pain and psychological symptoms, but the influence of these factors, assessed in the early posttraumatic period, has not previously been examined.

Material and Methods: Patients being evaluated in the emergency department (ED) after MVC were recruited into an ongoing multicenter study which includes ED baseline assessment, 3-7 day post-MVC assessment, and 1 month outcome evaluation. 3-7 day assessment includes brief versions of pain beliefs and coping strategies measures (i.e. SOPA; PBAPI; CSQ) and a brief assessment of social support (MSSS). One month outcome assessment includes evaluation of persistent MVC-related neck pain or back pain symptoms (each rated on a 0-10 numeric rating scale) and PTSD symptoms (IES-R). Associations between pain beliefs and coping strategies, social support and 1 month outcomes were assessed via correlation analyses.

Results: To date, follow-up data has been obtained in 48 of 49 enrolled patients who have reached the 1 month follow-up time point (98%, 28 female, 20 male, age 18-84, mean 36.4 years). Comparison of cognitive behavioral factors and 1 month outcomes are shown in table 1. Pain coping methods were strongly associated with both 1 month pain and psychological sequelae of MVC. Associations with 1 month pain outcomes persisted after adjusting for the severity of initial pain symptoms. There was no relationship between social support and 1 month pain or PTSD symptom outcomes.

Conclusion: These pilot data suggest that pain beliefs and coping strategies are predictive of pain and psychological sequelae after MVC. Updated information from this ongoing trial will be presented at the meeting.

Measure (Assessed 3-7 days after MVC[1])	Neck and Back Pain Severity 1 Month after MVC		Correlation with PTSD[3] Sympton 1 month after MVC assessed via IES-R[4]
Survey of Pain Attitudes Items[5]	Unadjusted r value (p value)	Adjusted for initial pain severity[2]	
Pain Control	-.317 (.038)	-.285 (.074)	-.471 (.002)
Disability	.453 (.002)	.464 (.003)	.409 (.007)
Harm	.146 (.350)	.100 (.541)	.217 (.167)
Emotion	.429 (.004)	.406 (.009)	.552 (.000)
Medication	.572 (.000)	.571 (.000)	.473 (.002)

Solicitude	.339 (.026)	.302 (.058)	.206 (.190)
Medical cures	-.494 (.001)	-.473 (.002)	-.258 (.099)
Pain Beliefs and Perceptions Inventory Items[5]	**Unadjusted**	**Adjusted for initial pain severity**	**PTSD Symptoms 1 month after MVC**
Mystery	.226 (.144)	.195 (.228)	.527 (.000)
Acceptance	.426 (.004)	.421 (.007)	.415 (.006)
Constancy	.511 (.000)	.467 (.002)	.451 (.003)
Self-Blame	-.239 (.123)	-.205 (.205)	-.226 (.151)
Coping Strategies Questionnaire Items[5]	**Unadjusted**	**Adjusted for initial pain severity**	**PTSD Symptoms 1 month after MVC**
Diverting attention	.042 (.788)	.103 (.528)	.014 (.930)
Reinterpreting pain sensation	-.089 (.569)	-.061 (.710)	.114 (.473)
Catastrophizing	.394 (.009)	.340 (.032)	.461 (.002)
Ignoring sensations	-.329 (.031)	-.284 (.075)	-.502 (.001)
Praying / Hoping	.274 (.076)	.227 (.158)	.216 (.168)
Coping self statements	-.101 (.521)	-.042 (.797)	-.090 (.572)
Increased behavioral activities	-.237 (.126)	.187 (.247)	-.302 (.052)

[1]Motor vehicle collision, [2]Global pain severity assessed in the emergency department using a 0-10 numeric rating scale, [3]Posttraumatic stress disorder, [4]Impact of Event Scale-Revised, [5]Brief version (Jensen et al 2003)